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Original Articles and Clinical Cases.

ON THE EXACT ORIGIN OF THE PYRAMIDAL TRACTS IN MAN AND OTHER MAMMALS.

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Little or no precise information can be obtained on the exact origin of the pyramidal tracts in even the later editions of the most authoritative text-books on the anatomy of the central nervous system.

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According to Edinger [10] "die Tractus cortico-spinales entstammen der Rinde der Zentralwindungen und des Paracentrallappens"; and Obersteiner's [23] account of their origin is as indefinite. According to Dejerine [8] they come from the upper five-sixths of the Rolandic convolutions, the neighbouring portions of the frontal and parietal gyri, and from the paracentral lobule. Von Monakow [20] writes: "Soweit meine eigenen mikroskopischen Erfahrungen reichen scheint die hintere Zentralwindung sich an dem Ursprung der Pyramidenbahn zu beteiligen, ebenso wie auch Abschnitte des Gyrus praecentralis," but "der Löwenantheil des Ursprungsgebietes der Pyramidenbahn in die vordere Zentralwindung, sowie in den Lobus paracentralis fällt."

In van Gehuchten's book [11] it is stated that the cells of origin of the pyramidal tracts occupy in the cerebral cortex "une zone nettement déterminée, appelée *zone motrice de Charcot*. Celle-ci est située autour de la fissure de Rolando et correspond à l'écorce grise de la circonvolution centrale antérieure, de la circonvolution centrale postérieure, du lobe paracentral, et de la partie voisine des circonvolutions frontales." Finally, Hoche [15] may be cited: "Das Rindengebiet von dem aus secundäre Degeneration der eigentlichen Pyramidenbahn erzeugt werden kann, umfasst die oberen zwei Drittel der Centralwindungen und das Paracentrallappchen; Fasern aus dem unteren Drittel, von der Insel, und aus den Centralwindungen unmittelbar anstossenden Teilen der Hirnswindungen stehen der Pyramidenbahn in Bezug auf Verlauf und Function sehr nahe."

From these extracts, and many others which might be quoted, it is evident that not only is the cortical origin of the pyramidal fibres not accurately known, but that the descriptions given of it are vague and discordant. It may be pointed out that all the above-quoted authors include the posterior central gyrus partly or wholly within the area of origin of the pyramidal fibres, and that none of them state from what cells of the cerebral cortex these cortico-spinal fibres actually arise.

Other authors have assumed that the origin of the pyramidal tracts is co-extensive with the so-called "excitable motor cortex"—the limits of which are still a matter of question—or with an area of cortex distinguished by certain structural peculiarities. And several, as Bolton [4] and Campbell [7], have gone further and assumed that the cortico-spinal fibres spring from certain characteristic cells which in distribution are limited to part of the "motor cortex"; but evidently the fact that certain cells are found only in a part of the excitable physiological area is, in itself, no proof that the chief efferent motor tracts take origin

from them. Schäfer [25] makes the statement that the giant Betz cells of the cortex give origin to the pyramidal tracts, and undergo chromatolysis after section of these fibres. Unhappily he does not describe the distribution of these cells, nor give references to the work on which his statement is founded.

Recognizing, then, how little is known of the exact origin of the pyramidal tracts, it seemed to us advisable to institute an investigation into the matter. Our main objects have been to determine:—

I.—From what regional area of the cerebral cortex the cortico-spinal tracts arise.

II.—From what cells of this region they take origin.

III.—Is the area of origin of the cortico-spinal tracts co-extensive with the so-called "excitable motor cortex"?

IV.—Does this area coincide with any "structural cortical field," such as has been mapped out in man and various mammals, especially by Campbell and by Brodmann?

II. Methods.

The method we have adopted has been to examine the cells of the cerebral cortex at some period after section or destruction of the cortico-spinal tracts. The period allowed to elapse between the division of these fibres and the sacrifice of the animal varied from five to 157 days; in the human cases investigated death resulted 108 and 229 days respectively after the accidents which divided the pyramidal tracts in the upper region of the spinal cord.

To insure accurate results it was evidently essential to use cases in which the pyramidal tracts were the only cortico-fugal fibres which were affected. In our experimental material, therefore, except in one lemur, the cortico-spinal tract of one side was divided by hemisection of the spinal cord in the higher cervical segments, and for investigation of the human brain we have employed only cases in which these tracts were interrupted by an acute transverse lesion of the spinal cord. Our human material has been restricted by the fact that to justify the conclusions we wish to draw it was necessary, in the first place, to use only cases in which there was a lesion completely interrupting all the pyramidal fibres; and, in the second, only cases in which the lesion was acute. The latter condition appeared necessary, as even in the peripheral neurones, in which they have been most carefully studied, the reactionary cell-changes on which we have relied in this work occur in their most typical form after acute axonal lesions, and they may not

appear at all, or only in modified form, when the interruption of the fibres has resulted from a slowly progressive lesion. In a later communication, however, we hope to show that the cortical changes which follow such spinal lesions, and those which are associated with many forms of system-degeneration of the upper motor neurones, entirely confirm the conclusions we shall state in the present paper.

Immediately after the sacrifice of each animal the brain was carefully removed, and the medial and lateral surfaces of both its hemispheres were photographed in natural size, or traced carefully and drawings made of them. In several cases the anæsthetized animal was transfused with physiological saline solution and immediately injected with one of the well-known fixatives before removal of the brain and its division into blocks. Thus the nerve-cells were actually fixed during life; the importance of this with regard to the subsequent examination of the minute structure of these cells can be scarcely sufficiently emphasized. In the remaining cases, after a preliminary hardening of the whole hemispheres, the Rolandic regions, including the anterior and posterior central convolutions and the neighbouring portions of the frontal and parietal lobes, were cut out and divided into suitable blocks, the position of each block being accurately marked on the corresponding photographs or drawings. In the carnivora relatively much larger areas of cortex, including the whole of the cruciate region, were treated in the same manner. Each of the blocks thus prepared was cut more or less completely into serial sections in either paraffin or colloidin, and each section was stained by some modification of Nissl's method.

In our experimental material the sections of the affected cortex—that is, that of the hemisphere of the opposite side to the spinal lesion—were carefully compared with sections from the corresponding parts of the opposite hemisphere; but as in our human cases both pyramidal tracts were destroyed, and therefore the cortex of each hemisphere equally affected, our sections could be compared only with those from similar regions of normal brains.

III.—Material.

The material on which our investigations have been carried out consisted of representatives of the carnivora—a dog and three cats—two lemurs, two monkeys of the macaque family, a chimpanzee, and two human brains from cases in which there had been severe traumatic lesions of the spinal cord. For comparison with the latter we have also examined the cortex of two cases with almost complete destruction of

the internal capsule and of part of the basal ganglia by lesions of vascular origin.

The nature and the characters of the histological changes we found, in one or other of the stages, in the cells of the cerebral cortex of all these animals may be briefly described here. They consisted essentially of that process which is generally known as retrograde chromatolysis or *reaction à distance*, but its salient features, as it was met with in these cells, deserves some notice.

The cells in which we found these changes and their cortical distribution will be fully described later; here it is only necessary to mention that the characteristic alterations were limited to the giant-cells which distinguish the infra-granular layer of large pyramidal cells of a small region of the cortex—in fact, to those which were originally described by Betz, and are now frequently known by his name.

After complete sections of one pyramidal tract in the higher cervical segments of the cord the changes in these cells appear relatively early. In a cat five days after this operation they were distinct though slight; in a few of the largest cells from the posterior wall of the cruciate sulcus of the opposite hemisphere there was slight disintegration of the tigroid clumps near the axonal origin and in the perinuclear zone. In a dog twenty-three days after the operation many of these cells were in advanced chromatolysis; their cell-bodies were more rounded than normal, the tigroid clumps were more or less disintegrated into fine granules, especially in the perinuclear and axonal regions, though the dendrites still contained many well-formed chromatophilic masses; their nuclei were generally eccentric and often irregular in shape, and a certain proportion of the cells were distinctly swollen, but the swelling of the cell-bodies was not a constant or very prominent feature. At this stage there was already some shrinkage or atrophy of some of the affected cells, and their dendrites began to disappear and break off. Cells in the more advanced stages of degeneration were frequently surrounded by several neurophages. Finally, even twenty-three days after the operation a considerable number of the affected cells had already disappeared, or only indistinct remnants of them were visible. In a cat killed twenty-nine days after hemisection of the left side of the cord changes similar, but somewhat further advanced, could be seen in the right cerebral hemisphere; here swollen cells were less numerous, the majority being shrunken and atrophic, and the proportional disappearance was much higher.

In a macaque monkey killed forty-nine days after spinal hemisection

the cortical changes were very similar to the above, but in another animal which was allowed to survive the operation 157 days the most prominent change was a great reduction in the number of giant-cells in the opposite hemisphere—in fact, only about one-thirteenth of the normal number could be seen; a few chromatolytic and degenerated forms were still visible.

In our human cases the cell-changes were more or less parallel to those we observed in our experimental material, but in relation to these a factor must be considered which appears to have an influence on the intensity of the chromatolysis and the rate of its course. This is the relative distance of the axonal lesion from the cell, or rather the relative amount of the axis-cylinder that is cut off from the cell by the lesion. It has been repeatedly observed by various experimenters that the reaction of the cell is more early and more intense the nearer the axis-cylinder is injured to its origin. In both our human cases the lesion lay in the seventh cervical segment of the cord, and consequently destroyed only the terminations of the cortico-spinal fibres which innervate the spinal centres for the wrist and fingers, but cut off relatively large portions of the neurone units which pass from the upper portion of the Rolandic region to the lumbo-sacral cord. This may be the explanation of the fact that in these brains the cortical cell-reactions were appreciably less intense and appeared later in the regions which we know send fibres to the cervical enlargement of the cord, than in those connected with the lumbar and sacral segments.

Although chromatolysis was the most characteristic change, it seems that a certain number of the affected cells merely atrophy and eventually disappear, some of the tigroid bodies persisting almost to the end. A smaller proportion, variable in different animals, undergo a pyknomorphic form of degeneration; these shrink but stain very intensely and almost uniformly, and the nucleus may be distorted, but is rarely, especially in the early stages, much displaced from its normal position near the centre of the cell.

Carnivora.

We have made use in this research of the nervous system of one dog and three cats.

Dog.—The animal was killed twenty-three days after section of the left side of the spinal cord in the first cervical segment. On microscopical examination it was found that the whole of the lateral column, the greater part of the dorsal column, and part of the ventral column

had been completely divided, while there was almost complete destruction of the rest of the left side of the cord by softening. The left pyramidal tract, as shown by the Marchi method of staining, appeared totally degenerated below the level of the lesion.

The cerebral cortex of the anterior half of each hemisphere was, after being divided into suitable blocks, cut into serial sections.

On the mesial surface of the right hemisphere the cell-changes were limited to a triangular area with its base, which measured 8 mm., on the apical margin of the hemisphere and its anterior edge along the bottom of the sulcus cruciatus almost as far, in this particular hemisphere, as its junction with the sulcus splenialis (fig. 1). The changes were entirely limited to the giant-cells of the infra-granular layer. These were, in the

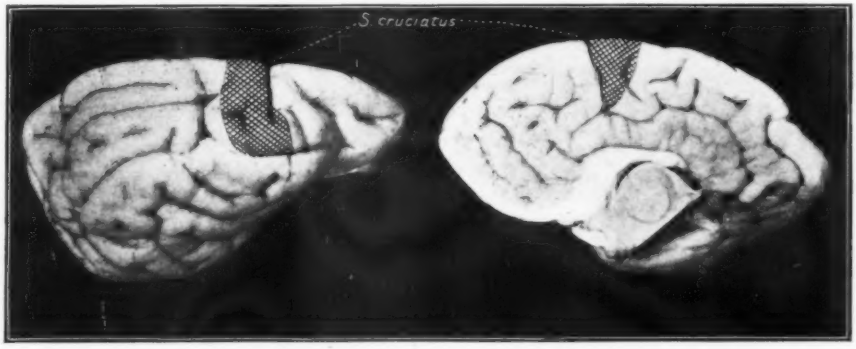


FIG. 1.
Photographs of the brain of the dog; the cross-hatched areas represent the origin of the cortico-spinal fibres.

first place, much less numerous than in the corresponding area of the opposite hemisphere; to determine the actual loss of these cells they were counted in a complete series of sections in both hemispheres. In the right—that is, in the affected side—all cells that could be recognized by a relatively low magnification were included, though, as will be shown, a considerable proportion of these were in some stage of chromatolysis. This enumeration revealed the fact that, even in the relatively short period that this animal survived the operation (twenty-three days), these cells were reduced to about a fourth or even less of their normal number. In a series of sections taken from near the upper margin of the left hemisphere, and parallel to it, the average number of giant-cells per section was 18·2, while in the exactly corresponding region of the other side

there were on an average only 3·5 in sections of the same thickness. Further, of these very few could pass as normal; almost all were in some stage of chromatolysis, but a few seemed small or shrunken with their nuclei distorted or misshapen. By examination with higher magnification the remnants of a considerable proportion of the more severely affected cells could be seen, generally only as faint shadows containing no chromatophilic material, and with only distorted and shrunken nuclei. Collections of neurophages were usually present around many of the cells in the more advanced stages of chromatolysis, but no inflammatory or vascular changes could be seen.

Repeated examination failed to discover such changes in any cells save the giant-cells of the infra-granular layer, which correspond to the Betz cells of the human cortex; no numerical loss of, or chromatolytic changes in, cells of any other variety could be detected. Owing to their size alone the affected cells cannot be mistaken, for the supra-granular layer contains no cells which are even relatively large, and in size, shape and structure the cells with which we are here concerned are characteristically different from the few large pyramidal cells of the layer in which they lie.

The superficial extent of the changes on the lateral surface of the hemisphere is best understood from fig. 1. It includes, approximately, the anterior two-thirds of the gyrus sigmoideus posterior; it does not extend anterior to the bottom of the sulcus cruciatus in the mesial half of this fissure, but further lateralwards it invades its anterior wall and appears on the gyrus sigmoideus anterior about 2 mm. from the lateral extremity of the sulcus. Beyond this the whole area, remaining about the same breadth, slopes somewhat forward and lateralward to the sulcus coronalis, beyond which no definite changes could be discovered. The amount of the anterior sigmoid gyrus which is affected is thus small. A considerable part of the affected area lies in the walls of the sulcus cruciatus. The changes which characterize this area were identical with those which have been described in the contiguous part of the mesial surface of the hemisphere, and the proportion of the cells affected was approximately the same. The changes were most pronounced in the posterior wall of the cruciate sulcus and in the anterior lip of the posterior sigmoid gyrus, in the regions in which the giant-cells are normally most numerous. Lateral to the extremity of the sulcus cruciatus the proportion of these cells which are unaffected appears to be somewhat larger.

The area we describe does not extend as far forwards as the small

precruciate sulcus, and in the intervening area, as well as in front of this fissure, large intact cells, similar in appearance to those which are affected, were present in considerable numbers. In this region—that is in the lower part of the gyrus sigmoideus anterior—the frontal limit of the affected area is not sharp or definite. Its posterior border, on the other hand, is fairly sharply defined; it coincides practically with the distribution of the giant-cells, though in the most lateral part of the posterior sigmoid gyrus, in the neighbourhood of the ansate sulcus, a small number of large cells remain unaltered.

No pathological changes were found in any other region of the cortex.

Cat 2.—Of the three cats which were operated on the most suitable for the detailed description of the resulting cortical changes was an animal which was killed twenty-nine days after section of the left side of the cord in the first cervical segment. The extent of the operative lesion was determined in serial sections; the whole of the left dorsal and lateral columns, and the greater part of the ventral column, were completely divided, and the only portion of the latter that escaped the cautery was softened. The right side of the cord, excepting a small strip of the dorsal column along the septum, was uninjured. The degeneration of the left pyramidal tract in the cord below the lesion was complete.

On the mesial surface of the right hemisphere the affected cortex occupied a triangular area between the margin of the hemisphere and the sulcus cruciatus, as well as the posterior wall of the latter. It extended about 4 or 5 mm. along the fissure—that is somewhat more than half-way to the level of the anterior extremity of the sulcus splenialis (fig. 2). The cell-changes in this area were of exactly the same nature as, but somewhat further advanced than, those in the dog. Here, also, only the large cells which characterize this region of the cortex were affected. These are, as compared with all the other cells of the cortex, enormous in the cat; many measure 30 by 50 μ, and even more. All these giant-cells were counted in serial sections in the left hemisphere, and thus the normal average number per section for each region was determined. The average number of normal cells, those showing any degree of chromatolysis being excluded, per section of the corresponding areas of the right hemisphere was similarly determined, and on comparison it was found that only from a fifteenth to a twentieth of the giant-cells of the right side were unaffected. In the anterior third of this area the average number of normal giant-cells per section was

12·6 in the left hemisphere, only 0·8 on the right; 10 and ·55 respectively in the middle thirds, and 7 and ·4 in the posterior thirds. The affected cells were in various stages of chromatolysis, and often only shadows or remnants were visible; the latter were often surrounded by clumps of neurophages, and small collections of these were occasionally the only indications of the positions from which chromatolytic cells had already disappeared.

The distribution of the pathological changes on the convexity of the hemisphere is best seen in fig. 2. At the apical margin its area lies entirely behind the sulcus cruciatus, but further lateralwards it crosses the bottom of this sulcus and appears on the anterior sigmoid gyrus, about 3 mm. from the mesial margin. From here its frontal margin advances lateralwards and frontalwards almost to the sulcus orbitalis.

FIG. 2.
The brain of a cat; the shaded portions represent the areas of origin of the cortico-spinal fibres.

The altered cells extend backwards almost, but not quite, to the sulcus ansatus, and lateralwards almost to the sulcus coronalis. This lateral margin, and especially its frontal part, was difficult to define, as here large numbers of normal cells appeared intermixed with others in chromatolysis. No definite changes could be recognized lateral to the sulcus coronalis.

The changes which characterized the area we have just defined were identical in nature and practically in degree with those discovered on the mesial surface. Between the margin of the hemisphere and the lateral extremity of the sulcus cruciatus only from 30 to 40 per cent. of the normal number of giant-cells were recognizable by a low magnification, and only about 6 per cent. or 7 per cent. of those present were unaffected, the remaining being in various stages of chromatolysis.

Beyond the lateral extremity of the sulcus cruciatus the proportion of normal cells rose considerably, and towards the lip of the sulcus coronalis it reached about 25 per cent.

Repeated careful examinations of our sections has confirmed our first observations—that it was only the giant-cells of this area which were unaffected; no numerical loss could be detected in the other layers of the cortex, and none of their cells were seen in chromatolysis.

Prosimia.

Two lemurs (*L. catta*) were operated on. In the one the cord was hemisected in the first cervical segment; in the other the left crus was divided. The latter animal proved especially valuable for the purpose of our present research. Immediately after the operation in this case the paralysis of the limbs and trunk of the side opposite to the lesion was almost total, and return of movement occurred much more slowly than in any of our other animals; slight and steady improvement, however, continued till the animal was sacrificed twenty-five days later.

Before death the cortex of each hemisphere was experimentally investigated by electrical stimulation, using both the bipolar and unipolar methods. Though muscular responses were readily obtained by excitation of the appropriate area of the right cerebral cortex (as previously delimited by one of us (W. P. M.) in several other lemurs), no movements whatever could be obtained even by unusually strong currents from any part of the hemisphere of the same side as the divided crus. At the autopsy it was found that the left crus had been completely divided. Systematic histological examination of the cortex of each side was carried out exactly as in our other animals.

Well-marked and characteristic changes were found in the cortex of the cerebral hemisphere on the same side as the divided crus; in fact, scarcely a single normal giant-cell could be found, almost all being in a well-marked or advanced stage of chromatolysis. Moreover, the number of these giant-cells was reduced to about the proportion of seven to sixteen, as compared with the healthy side. In spite, however, of this well-marked affection of the giant-cells, it was by no means easy to delimit accurately the area that contained them, for in the lowly differentiated prosimian brain there is a remarkable absence of definite sulci in immediate relation with the motor area. The most important landmark—which we shall speak of as sulcus x^1—is often merely a super-

[1] Homologue of the upper part of the Fissure of Rolando, according to Elliot Smith; the sulcus centralis of Ziehen.

ficial depression, and not infrequently asymmetrically placed in the two hemispheres, or even absent on one side. Further, the affected cells become much less numerous towards the confines of the area, and so sparse and so irregularly scattered that it is difficult to draw a line of demarcation that shall include them all without enclosing small portions of unaffected cortex. The area shown in fig. 3 is, however, sufficiently definite, and includes practically all the affected cells. On the mesial surface it does not extend quite to the callosomarginal fissure, and on the lateral surface it lies almost entirely in front of sulcus x, which, however, it just includes. Affected cells are more numerous in the anterior than in the posterior wall of this sulcus, and very few giant-cells in chromatolysis could be found behind its posterior lip. The area definitely crosses the sulcus frontalis, narrowing as it descends,

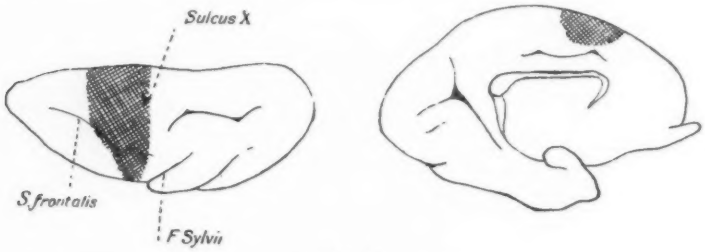


FIG. 3.
The brain of *lemur catta*; the shaded portions represent the areas in which cortical changes were found secondary to section of the left crus cerebri.

and almost reaches the sylvian fissure, but its lateral limit is, for the reasons given above, not sharply definable.

In addition to this affection of the giant-cells similar changes were found in a certain number of the ordinary large pyramidal cells of the supra-granular, but more especially of the infra-granular, layers; the affection of these cells was much wider spread than the area which contained giant-cells. The significance of the involvement of these large pyramidal cells will be discussed later.

The Gyrencephalic Monkeys.

Two animals of this class were used for this investigation.

(1) *Cercopithecus callithrix*—The animal was killed 157 days after section by the electro-cautery of the right side of the spinal cord in the first cervical segment. Immediately before it was sacrificed the "motor"

cortex of both hemispheres was investigated under anæsthesia by means of a faradic current, and with the usual precautions. Both the unipolar and bipolar methods were employed. Movements of the left limbs were easily obtained by excitation of the right anterior central gyrus, but to currents of the same strength the posterior central gyrus gave no muscular response. No movements of the limbs could be produced from the corresponding regions of the left hemisphere by a current of this strength,

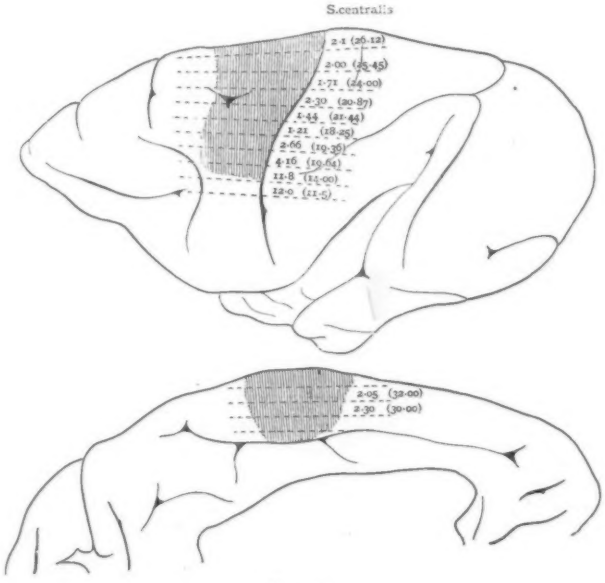


FIG. 4.

Tracings from photographs of the lateral and mesial surfaces of the brain of *cercopithecus callithrix*; the shaded portions indicate the areas in which cortical changes were found after section of the right side of the spinal cord in the first cervical segment. The figures represent the average number of giant-cells per section found at the different levels in this hemisphere; those in brackets the average number per section at the corresponding levels of the opposite hemisphere.

but slight movements of the homo-lateral (left) toes were obtained by the application of a considerably stronger current to the pre-central gyrus above the level of the precentral sulcus, and similar excitation of the gyrus between this level and the bend of the sulcus arcuatus elicited slight movements in the elbow, wrist and fingers of the same side.

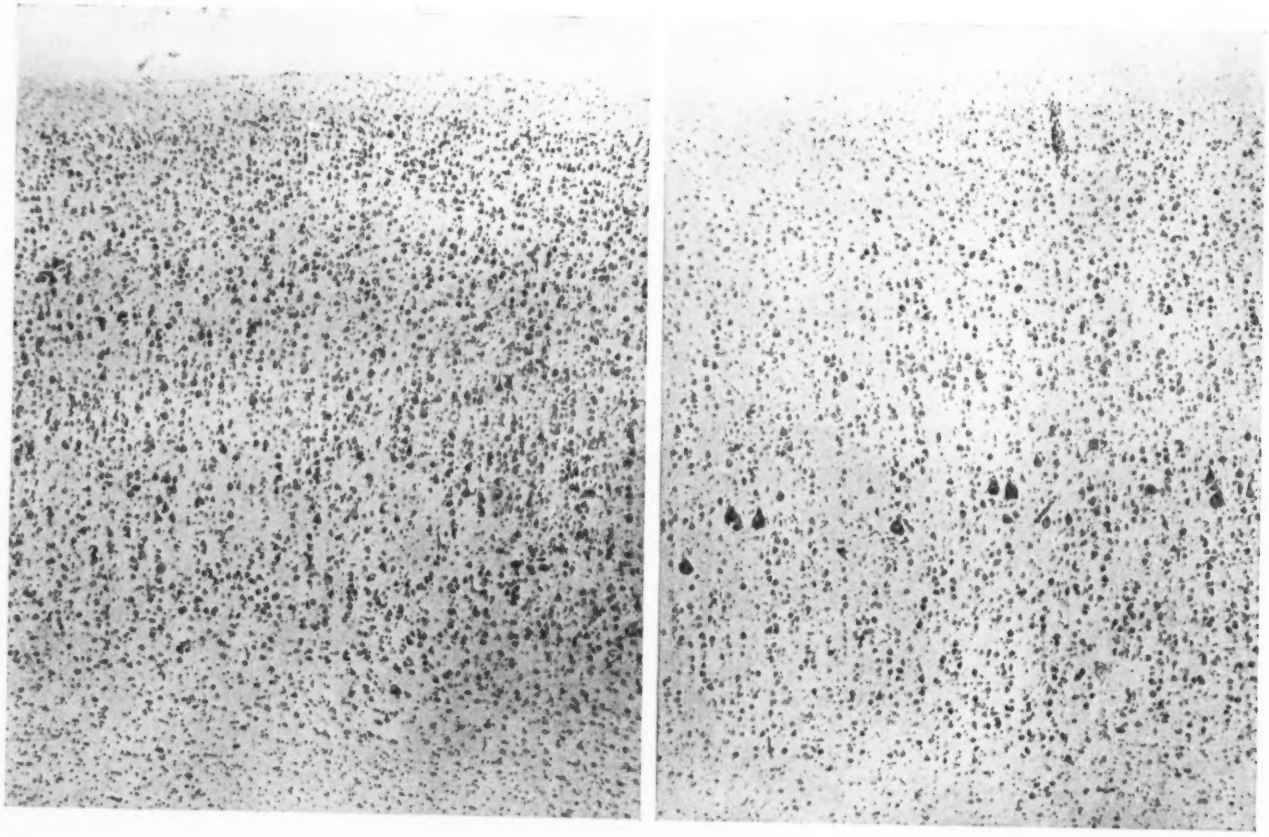
The operative lesion involved practically the whole cross-section of the right side of the cord.

The anterior and posterior central gyri, with the greater part of the frontal lobes and the contiguous portion of the medial surface of both hemispheres, were studied in serial sections stained by thionin. The distribution of the changes which were found in the left hemisphere is represented in fig. 4. On the medial surface it lay between the margin of the hemisphere and the callosomarginal sulcus, extending frontalwards about 13 mm. from the upper end of the sulcus centralis; the area narrowed considerably towards the callosomarginal sulcus, being here scarcely half as broad as at the margin. On the lateral surface it extended to about the level of the genu of the sulcus arcuatus, or to a line drawn from its angle to the extremity of the sulcus intraparietalis. At the apex of the hemisphere its posterior border fell practically along the bottom of the sulcus centralis, but lower it receded slightly from it, ascending the anterior wall of the sulcus. The anterior margin extended from a point on the apex of the hemisphere about 13 mm. in front of the sulcus centralis to the knee of the sulcus arcuatus; the sulcus precentralis superior was included within it.

The most striking change in this area was the enormous reduction in number of the giant-cells of the infra-granular layer. To determine accurately the degree of this change the giant-cells of the right hemisphere were counted in several series of sections, and those persisting in the left were enumerated in the same manner. By comparison of the numbers so obtained from corresponding regions of the two hemispheres it was evident that only from a fifteenth to a twelfth of the normal number persisted in the affected area on the left side. Here and there throughout this area a few remnants of degenerated cells were visible, but they were rare; they generally appeared as shrunken palely staining structures with distorted and often protruding nuclei, and were frequently surrounded by neurophages. Occasionally degenerated cells were represented only by a mass of pigment, and often their site was recognizable only by a group of neurophages, which were generally laden with nerve-cell pigment (fig. 5).

Despite this remarkable affection of the giant-cells we could detect absolutely no change in the ordinary large pyramidal cells of the supra- or infra-granular layers of the cortex of this region, or in the cells of any other layer. There did not appear to be, even on careful comparison with the normal, the slightest reduction in the number of these cells, and no remnants or degenerated forms were visible other than those described above.

The changes appeared to be entirely limited to the area we have



B. *A.*

FIG. 5.

A, a microphotograph of the normal precentral cortex (area gigantopyramidalis) of the macaque monkey; B, from a section in a corresponding part of the left hemisphere 157 days after division of the right side of the spinal cord; only the indistinct remnants of two giant-cells are visible.

defined; certainly no part of the cortex posterior to the sulcus centralis was in any way affected.

(2) *Macacus rhesus.*—The animal was killed forty-nine days after section of the left side of the spinal cord in the first cervical segment. When examined in the micrōscopical sections it was found that the lesion had almost completely severed the left side of the cord, while of the right side it injured only a small portion of the dorsal columns. The degeneration of the left pyramidal tract was complete below the lesion. The examination of the cortex was undertaken in the usual way, the region of each hemisphere systematically examined including the anterior and posterior central gyri and the greater part of each frontal lobe.

The area in which the characteristic changes were found corresponded closely to—in fact was almost identical with—that mapped out in the previously described animal (fig. 6), though its superficial extent on the surface of the hemisphere was scarcely so broad; at the apical margin it reached 11 mm. in front of the upper extremity of the sulcus centralis. It extended downwards along the sulcus centralis almost to the genu of the sulcus arcuatus, not quite to a line connecting this with the extremity of the sulcus intraparietalis. The details of the changes which mark out this area differed considerably from those described in the callithrix monkey, owing to the much shorter period the animal was allowed to survive the operation; they consequently resembled more closely those we have described in the dog and cats which were killed a much shorter time after the operation.

There was, in the first place, a considerable reduction in the number of the giant-cells of the infra-granular layer; on an average only between a third and a half of the normal number persisted, even including in our enumeration several which were in advanced stages of chromatolysis. The actual number of intact cells was small, approximately the same as in the callithrix monkey—that is, only about, or less than, a twelfth of the normal. The affected cells were, as a rule, in advanced chromatolysis, with complete dissolution of the tigroid clumps and excentration of the nucleus, but very few were swollen; in fact, many were shrunken and atrophic. In many places the degenerated remains of cells could be seen surrounded by neurophages.

As in the specimens previously described, it was only the giant-cells of the infra-granular layer of the cortex which were affected; in such a case as this in which chromatolysis was the predominant change it would have been scarcely possible to fail to detect the specific change in

any of the other cells if they had been similarly altered. In this specimen, too, there could be no doubt that the characteristic changes did not extend to the cortex on the posterior wall of the sulcus centralis, or to that covering the posterior central gyrus.

Chimpanzee.

Two animals were operated on by one of us (W. P. M.) in the Physiological Laboratory of the University of Liverpool; we wish to record

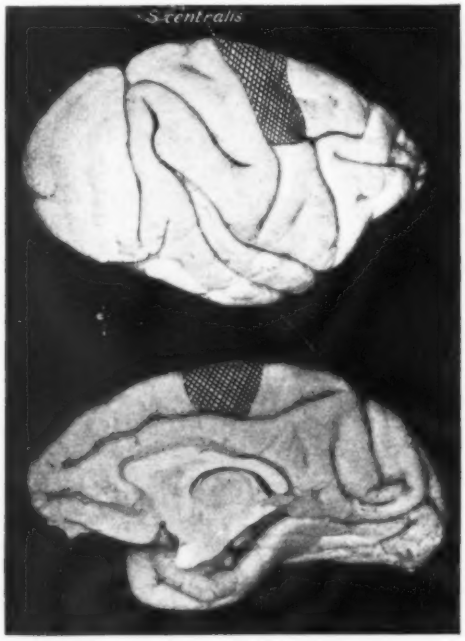


FIG. 6.

The brain of a macaque monkey, the shaded areas representing the regions in which cortical changes were found after division of the left side of the spinal cord in the first cervical segment.

our cordial thanks to Professor Sherrington, who kindly gave his valuable help at these operations. In each the lateral pyramidal tract was completely divided in the third cervical segment of the cord, but, unfortunately, though both operations were successful, one of the animals died on the third day from influenza. The second animal made a complete recovery, and was allowed to survive exactly four weeks.

Immediately after the operation there was total paralysis of the arm and leg on the side of the lesion, and serious interference with the movements of the same side of the trunk. But in about thirty-six hours a visible return of power began to set in and steady improvement continued for four weeks, when to a layman the animal would have seemed in possession of all ordinary power of movement; walking was apparently normal, and the affected forelimb was used in climbing and not infrequently in taking food. The vasomotor and sensory phenomena which resulted from the lesion need not be considered here.

Twenty-eight days after the operation the animal was again placed under chloroform, and the cortex of both cerebral hemispheres was investigated by electrical stimulation during some five or six hours. Both the unipolar and bipolar methods of stimulation were employed, and by a simple arrangement it was made possible to employ the same battery and secondary coil for either method at any moment, so that exactly the same strength of current could be applied as desired through either the unipolar or bipolar electrode.

Stimulation of the motor cortex of the hemisphere of the same side as the spinal lesion gave results which agreed closely with the classical researches of Grünbaum and Sherrington [13] on the anthropoid apes. Further details of this particular investigation will be given in another place, but here we may say that no response whatever was obtained from any part of the posterior central gyrus, and that the area which responded to stimulation by a minimal current was limited to the anterior central and the paracentral gyri, and to the immediately adjoining portions of the superior and middle frontal convolutions. From the cortex of the other cerebral hemisphere—that contra-lateral to the spinal lesion—no movements of the limbs of either side, or of the trunk, could be obtained during the first three hours of stimulation, but after that time, when the cortex was presumably passing into a state of greater excitability, slight movements of the contra-lateral toes, knee and hip were obtained, and also, but to an even less degree, of the shoulder and fingers.

Homo-lateral movements could not be elicited from either hemisphere. In view of the almost complete return of voluntary power after the previous paralysis, contrasted with the difficulty of eliciting even slight movements by electrical stimulation of the affected cerebral cortex, it is evident that there must be an essential difference between the elicitation of movements by volition, and by electrical excitation of the cerebral cortex.

It must be pointed out that in this animal only that portion of the cortico-spinal tract that runs in the right lateral column (the crossed

pyramidal tract) was divided; the uncrossed tracts of the ventral columns escaped, and as they were not degenerated we have no means of estimating what proportion of the cortico-spinal fibres they contained. Grünbaum and Sherrington have shown that the ventral pyramidal bundles are present and as variable in the higher apes as they are in man; as they do not exist in monkeys or in animals lower in the scale, reference to them was not necessary in our accounts of those animals.

In this chimpanzee, as in our other animals after spinal lesions, reactionary chromatolysis could be detected only in the giant pyramidal cells of the cerebral cortex, and they were almost entirely limited to the hemisphere of the side opposite to the spinal lesion. We searched carefully for similar changes in other cells, but though a few of the ordinary large pyramidal cells presented nuclei displaced towards the periphery, and occasionally a partial absence of tigroid bodies in the neighbourhood of the nuclei, we could not convince ourselves that there was here any definite chromatolysis. It may be noted that the giant-cells of the chimpanzee brain are of very various sizes, some of them scarcely exceeding in bulk the ordinary large pyramidal cells; but though none of the latter were affected, changes could be seen in giant-cells of all sizes. This fact is of interest, for, as will be shown later, it is these giant-cells which give origin to the cortico-spinal fibres, and they vary considerably in calibre in the spinal cord.

Careful enumerations of the giant-cells of each hemisphere were made, and on comparison it was found that those of the left cortex were considerably reduced in number, to the proportion of about four to seven as compared with the opposite side. Further, the interesting fact came out that while in the leg and body areas the giant-cells in chromatolysis were about four times as numerous as the unaltered cells, in the forearm and hand areas the proportion of the affected to the unaffected giant-cells was as seven to one. This fact may be possibly correlated with the greater bilateral representation of the lower limb and trunk movements, but as the direct ventral pyramidal tracts were not divided, it seems that in the upper cervical segments of the cord the cortico-spinal fibres which subserve the leg and body are relatively less numerously represented in the lateral (crossed) pyramidal tract than those subserving the forelimb, whereas in the direct pyramidal tracts the converse obtains.

The area delimited by these affected cells is indicated in fig. 7. It lay immediately in front of the fissure of Rolando. On the mesial surface of the hemisphere it assumed the shape of a flattened inverted pyramid which just extended down to the callosomarginal sulcus. On the lateral surface

it was limited posteriorly by the characteristic structure of the posterior central gyrus, which, in the upper part of the hemisphere, coincided almost exactly with the floor of the central fissure; but, more laterally, the affected area receded more and more from the floor of this fissure—that is, it ascended the anterior wall of the sulcus, in proportion with the increased distance from the middle line. In the many hundreds of

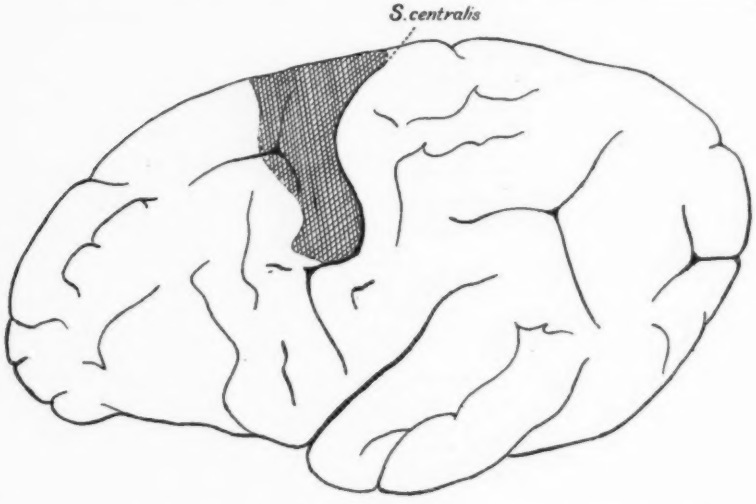


FIG. 7.

The lateral surface of the brain of a chimpanzee showing the region in which cortical changes were found after section of the cortico-spinal fibres in the right side of the spinal cord.

sections examined in this animal not a single affected cell was found posterior to the floor of the fissure of Rolando. In the upper part of the lateral surface the area included the whole of the precentral gyrus and a considerable portion of the frontal lobe immediately anterior to it, but its lower part extended only just across the anterior central gyrus.

The cell-changes cease almost abruptly just above the inferior genu of the central fissure, for in sections immediately below this not more than one in every fifty cells was affected, and even these disappeared in the space of 2 mm. or 3 mm.

Human Cases.

Although the cortex of the Rolandic region of the brain has been systematically examined by one of us (G. H.) in a large number of cases

in which the pyramidal tracts had been involved in local lesions or system degenerations of the spinal cord, the only material of which we shall make use in our present communication was obtained from two cases in which there was complete or almost complete destruction of these tracts by traumatic lesions of sudden onset. By excluding cases in which the disease was slowly progressive, and the interruption of the fibres therefore not sudden, we are in less danger of adopting conclusions not warranted by facts.

Case 1.—B. C., aged 17 years, was admitted to St. Bartholomew's Hospital under the care of Mr. W. Bruce Clarke, to whom we are indebted for permission to use the case, with a fracture-dislocation of the vertebral column in the lowest cervical region. The injury was received in a lift accident. After recovery from the shock it was ascertained that there was complete loss of all forms of sensation below the cutaneous distribution of the seventh cervical roots, with complete paralysis of the lower extremities and trunk as well as of the movements of the fingers and wrists. The shoulder movements were unaffected. Flexion, supination and pronation of the elbows were possible, but were considerably weaker in the left than in the right limb; the right elbow could be extended very weakly, but on the left side this movement was completely paralysed. Death occurred 229 days after the accident.

Dr. Hinds Howell, who examined the spinal cord, has kindly given us the following report: "There was a complete transverse lesion of the cord in the seventh cervical segment; no fibres pass through this level intact. The lesion extends higher on the left than on the right side, reaching the lowest part of the sixth segment. Such a lesion naturally produced total degeneration of the pyramidal tracts below its level."

The brain was received hardened in formalin. The hemispheres were photographed and the whole of the Rolandic region of each, with the paracentral lobules, was divided into suitable blocks, the position of each block being carefully marked on the photographs. The sections obtained from each block could be thus accurately localized. They were stained with thionin.

Identical changes were found in both hemispheres. In the paracentral lobules in front of the upper extremity of the fissure of Rolando there was a practically complete disappearance of the large giant-cells which characterize this region; in numbers of serial sections not a single one could be seen, and on the right side in which all present were counted there were not more than two or three in every twenty sections,

and almost all of these were degenerated; the normal average number of giant-cells per section in this region is about thirty. The majority of the cells had disappeared without leaving a trace of their previous existence, but here and there masses of pigment, or small clumps of neurophages, or of glial nuclei marked the positions they had occupied. Despite this extraordinarily severe affection of the giant-cells of the infra-granular layer we could detect no pathological change in, or numerical reduction of, the ordinary large pyramidal cells of the infra-granular or supra-granular layers; the polymorphic layer and the layers of small and medium-sized pyramids also appear to have escaped entirely. The extent of the area in the paracentral lobules which shows this change is represented in fig. 8.

The same pathological condition was found on the lateral surface of the brain near the apex, but about 15 mm. from the latter, measured along the fissure of Rolando, giant-cells begin to reappear, at first in very small numbers, but their number increased gradually lateralwards. The majority of these cells, however, were far from normal; some were in the advanced stages of chromatolysis, others were represented only by atrophied and shrunken remains. At about 20 mm. from the apex, still above the level of the superior frontal sulcus, there was in the space of a few millimetres a great increase in the number of normal cells, and degenerated and atrophied ones disappeared from the sections. The transition of the abnormal to the normal cortex can be scarcely described as abrupt, as through the space of a few millimetres normal and degenerated cells were found together, but it could be certainly easily defined.

Immediately below this area there came a strip of cortex on the anterior wall of the fissure of Rolando and on the anterior central gyrus, the structure of which was normal; it contained the standard number of giant-cells. But at a level which was approximately opposite the middle of the second frontal convolution the giant-cells again became less numerous than normal, and many of them were atrophied or in chromatolysis. The transition here between the cortex which was normal and that which was affected was, however, quite gradual; and the pathological changes in this area were not so marked as in the paracentral lobule and the upper third of the anterior central gyrus. The giant-cells were nowhere reduced to less than a third of their normal number, and a certain proportion of them were intact. The extent of this area of pathological cortex is represented in fig. 8; its lower margin could be more easily delimited than its upper, but it was

by no means sharp. The distribution of these changes along the fissures of Rolando was the same on the two sides.

The topography of this affected area on the lateral surfaces of

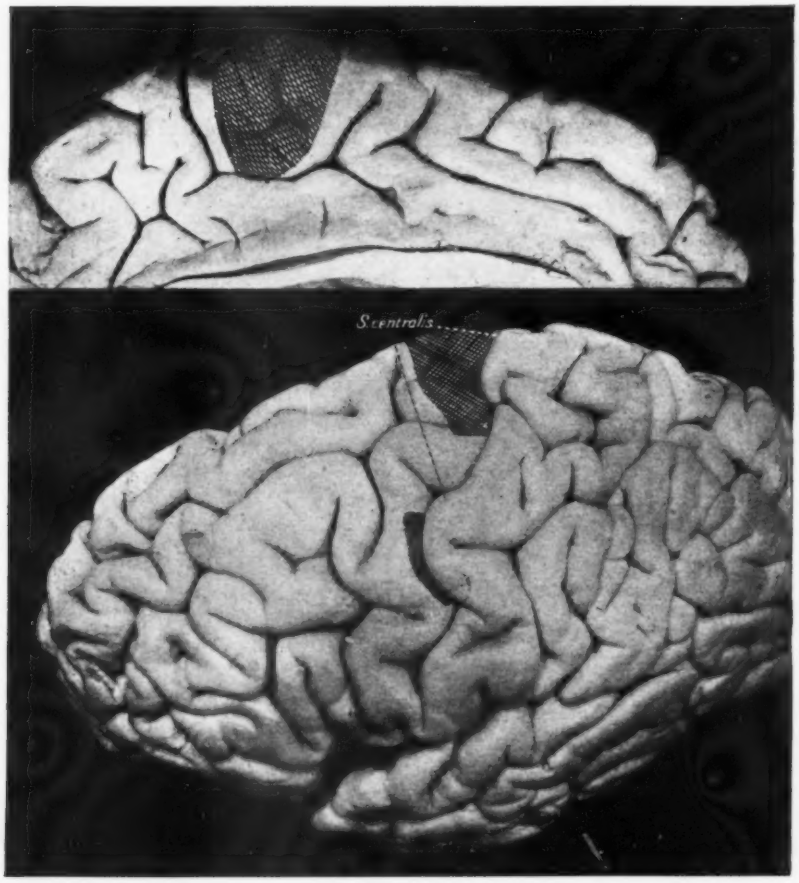


FIG. 8.

Photographs of the brain of Case 1. The shaded areas represent the regions in the surface of the brain in which cell-changes were found.

the hemispheres may be briefly described. Its posterior margin coincided practically everywhere with the bottom of the fissure, but it is interesting that at least many of the large cells which resemble

the "Betz" cells in size, but lie within the oral limit of the post-central cortex—in the "transition area" of Brodmann—were not affected. The anterior limit of the area is most easily understood from our illustration; it must be, however, added that in the lower area the greater part of the altered cortex was hidden in the fissure of Rolando, and only a relatively small portion of it appeared on the convexity of the anterior central gyrus.

Absolutely no histological changes could be detected posterior to the fissure of Rolando, in front of the frontal edge of our areas, or in any other region of the cerebral cortex.

Case 2.—A woman, aged 68, suddenly lost the power of movement in her lower limbs and hands after a fall on her back. On examination a few days after the accident there was complete loss of power in the lower extremities and trunk muscles, as well as incontinence of urine and fæces. The movements of the shoulder-joints were unaffected, and flexion of the elbows was possible, though weak; there was almost complete paralysis of the extensors of the elbows and of all the movements of the wrists and fingers. This condition improved very little before death, which occurred 108 days after the accident. We are indebted to Dr. J. R. Lunn for this case.

The spinal lesion was found on *post-mortem* examination between the sixth and seventh cervical segments at practically the same level as that in Case 1. The dorsal columns, the dorsal horns, and the whole of the right lateral column excepting its periphery were completely destroyed at this level, and the lesion also extended into the left lateral column probably far enough to interrupt almost the whole lateral pyramidal tract. On examination of the cord by Marchi's method there seemed to be below the lesion complete degeneration of the right crossed pyramidal tract, but the degeneration was not so great in the left lateral column. As the lesion was limited to the dorsal half of the cord the direct pyramidal tracts of the ventral columns escaped, and we had no means of estimating the proportion of the cortico-spinal fibres these carried in this case.

The examination of the cortex was conducted in the usual way. The description of the changes we found may be limited to the left hemisphere, as they were more pronounced on this side than on the right, but were similar in both except in degree.

The normal giant-cells were counted in series of sections from about every 2 or 3 mm. along the fissure of Rolando, and the average number per section at various levels was thus obtained. These, when compared

with the numbers from the corresponding levels of normal hemispheres, gave a fair indication of the relative affection of the cortex at different levels. In the paracentral lobule the affected area lay entirely in front of the upper extremity of the fissure of Rolando; it contained only about 2·5 intact giant-cells per section, while the normal average is about 30. In every section large numbers of giant-cells in chromatolysis could be seen, and a striking feature was the great excess of pigment all the affected cells contained. This pigment was present in unusual amounts in many of the giant-cells which have been included in the normal count, as considering the age at which the patient died its presence, unless associated with disintegration of the tigroid and displacement of the nuclei, was not regarded as evidence of degeneration. Often only masses of pigment without any stainable cytoplasm or a nucleus represented degenerated cells, and not infrequently clumps of neurophages laden with such pigment could be seen. Only the giant-cells of the infra-granular layer were affected, and it is noteworthy that there was no great excess of pigment in the other cells of the cortex.

On the lateral surfaces of the hemispheres the areas of affected cortex were practically identical with those mapped out in Case 1. From the mesial margin to about the middle of the superior frontal gyrus the relative reduction of the giant-cells was practically the same as in the paracentral lobule, but here a transition area appeared which contained both normal and pathological cells, the proportion of the former increasing as sections were examined from above downwards. A short distance above the level of the superior frontal sulcus chromatolytic and atrophic cells disappeared, and an area of normal cortex covered the precentral gyrus to just below the inferior genu of the fissure of Rolando. From here for a distance of about 15 mm. along the fissure there was another definitely abnormal area of cortex in which the giant-cells were considerably diminished—to about half of the normal—and many which persisted were in chromatolysis. The topography of this area was practically the same as in Case 1, and, as in that specimen, the transition from the normal to the abnormal cortex was not by any means abrupt or sharp; consequently a definite line could not be drawn around the area. The cortex of the lower quarter of the anterior central gyrus was intact.

The posterior limit of the affected areas on the lateral surfaces of the hemispheres fell along the bottom of the fissure of Rolando; the anterior limit can be best understood from fig. 8. From this it is evident that the greater part of the lower area lay in the anterior wall of the

fissure of Rolando. Absolutely no changes could be detected in the cortex behind this fissure, or in any other region of the brain.

The Cortical Changes which Result from Capsular Lesions.

A short description may be given here of the cortical changes which were found in cases in which the internal capsule as well as part of the central ganglia had been destroyed some time before death, but as lesions in this region must interrupt, in addition to the pyramidal tracts, projection-fibres from other regions of the cortex the facts we have obtained from these cases have less direct value for the problems we attempt to solve.

Case 3.—A female, aged 26, died six weeks after the onset of a right hemiplegia, which was due to vascular embolism and a softening which destroyed the left internal capsule, and almost the whole of the nucleus lenticularis and of the optic thalamus.

The cortical changes were of interest, especially in contrast to those we found secondary to spinal lesions. Throughout the whole of the left anterior central gyrus and the paracentral lobule there was a considerable diminution of the giant-cells which characterize this region, and very few of those persisting were normal. The majority were in chromatolysis or typical *reaction à distance;* the swelling of the cells and the excentric position of the nuclei seemed to be a more prominent feature than in the reaction of these cells to spinal lesions. The disintegration of the tigroid bodies was complete in most of the affected cells, in many the dendrites were shrinking or had disappeared, and some cells were already represented only by masses of pigment.

These changes were not, however, confined to the giant-cells or to the areas in which we detected cortical cell-changes after spinal lesions. In addition to the giant-cells many of the ordinary large pyramidal cells of the infra-granular layer, and a smaller proportion of the supra-granular or superficial pyramids, were similarly affected, and it could be ascertained beyond doubt that a considerable proportion of the former had disappeared. No changes could be detected in the more superficial layers of the cortex, or in the layer of polymorphic cells.

Further, these changes were not limited to the precentral area; in the posterior central gyrus, and indeed in all parts of the cortex which were examined, a not inconsiderable proportion of the infra-granular pyramids and a smaller proportion of the superficial pyramids were in chromatolysis, and in most regions it appeared probable that many of

the larger cells of the deeper layer had disappeared. Unfortunately the whole of the cortex of this hemisphere was not systematically examined.

This affection of the cortical cells can scarcely have been a direct result of the vascular lesions, as the softening did not extend into the cortex, and it was quite as prominent in the paracentral lobule and at the apex of the hemisphere, both of which receive their blood-supply from the anterior cerebral artery, as in the area of distribution of the middle cerebral artery.

Case 4.—A man, aged 41, had a stroke producing a right hemiplegia about eighteen months before his death. Part of the left internal capsule was destroyed with portions of the central ganglia; the degeneration of the cortico-spinal fibres was so complete that the left bulbar pyramid was practically devoid of myelinated fibres.

The chief cortical changes were: (1) almost complete absence of giant-cells from the precentral cortex; (2) a definite loss of the ordinary large pyramidal cells of the infra-granular layer in both the precentral and the postcentral cortex, with increase of neuroglia throughout this layer; and (3) possibly some cell-defect in the superficial layer of large pyramidal cells, but on this it was extremely difficult to decide with certainty.

A short summary of our observations may be given in a few sentences. By making use of the reactionary chromatolysis and the subsequent changes which occur in nerve-cells after division of their axis-cylinders, we have been able to determine the cortical cells which react to section of the cortico-spinal tracts, and from which we must assume, therefore, that these fibres take origin in man, the chimpanzee, certain monkeys, the lemur, and in representative carnivora.

In the primates (man, ape, and monkey) the area which contained these cells lay entirely in front of the sulcus centralis; in the carnivora it was in less close relation to any sulcus, but it was chiefly behind the sulcus cruciatus.

Further, the only cells from which we have been able to show that cortico-spinal fibres spring are the giant-cells of the infra-granular layer, which characterize this region of the cortex in all the mammals we have used in this investigation.

Before discussing the significance of these observations, and the conclusions that may be drawn from them, it is advisable to give a short review of the more important contributions to our subject that have been already published. But very few of these deal directly with the origin of the pyramidal tracts.

Several authors have directed attention to the alterations of the cells of the cerebral cortex which follow lesions of the internal capsule. von Monakow [20] writes that "all the giant-cells (Riesenpyramiden) in both man and animals degenerate after the destruction of the internal capsule," and "the pyramidal tracts take origin from the giant-cells of the central convolutions" (S. 198); but there can be no doubt, from his text and his illustrations (*see* his fig. 113), that in this connection he applies the term "Riesenpyramiden" to the large cells of the supra-granular layer; in fact, the giant-cells of Betz are not found in both central convolutions, but only in the anterior. Dotto and Pusateri [9] have also observed degeneration of the cortical pyramidal cells after destruction of the internal capsule; and Marinesco [17] has recorded the cortical changes he found in six cases associated with capsular lesions of variable duration. These alterations included chromatolysis, atrophy, or disappearance of the large pyramidal-cells, dependent on the duration of the lesion before death. It is not, however, evident from his paper if it was only the large giant- (Betz) cells that he saw affected, and he has not described definitely the area in which these changes were present. At about the same time Ballet and Faure [2] demonstrated the *reaction à distance* in the large cortical pyramidal-cells in dogs after subcortical section of the projection-fibres; and more recently Gentès and Bellot [12] have studied the alterations in the neurofibrils of these cells that occur secondary to destruction of the internal capsule in man. In neither of the last-mentioned papers is the region in which these reactionary changes were found, or the cells which were affected, accurately described. But, despite the intrinsic interest of these observations, it is evident that no conclusions as to the origin of the pyramidal tracts can be drawn from them, as when these are completely destroyed in the internal capsule many of the projection-fibres which pass from the cerebral cortex, as well as the cortico-pontine tracts, must be also interrupted, and the cells from which these take origin would consequently show the same changes as those from which the cortico-spinal fibres arise.

In a later communication Marinesco [18] has described the cortical changes he discovered in six cases of paraplegia due to local spinal lesions. The cell-changes were described as limited to the paracentral lobule and the upper third of the anterior central gyrus, and only the giant-cells of this region were affected. The chromatolytic changes supervened later and were slower in their course than those which resulted from interruption of the fibres of the internal capsule. It is interesting

that Rothmann [24], in the discussion which followed the presentation of Marinesco's paper, stated that four weeks after transverse section of a dog's spinal cord "the cortical cells were completely normal"; but it is not clear if attention was specially directed to these, or what parts of the cortex were examined.

The first deliberate attempt to define the exact origin of the cortico-spinal tracts has been made by Campbell [7] in connection with his work on the histological localization of cerebral function. This author came to the conclusion at which we have arrived, in fact he regarded "the Betz cells as discharging elements for motor impulses," but the arguments upon which he relied were scarcely sufficient to support this conclusion. In the first place, he made use of the cortical changes he found in two cases of amyotrophic lateral sclerosis; he writes of this as "a disease limited in its affection to the muscular system and the motor systems of neurones," and consequently argues that the fact that the cortical changes he discovered were limited to the precentral area "constitutes the strongest confirmatory evidence yet adduced to support the assumption that in man, as well as in the anthropoid apes, the elements acting for the direct control of muscular movements are confined to the precentral gyrus and its paracentral annexe." But, unhappily, his premise is absolutely inaccurate, as amyotrophic lateral sclerosis, as is now well known, is not a disease limited to the motor systems of neurones—in fact, in a series of ten cases examined by one of us (G. H.) there was invariably only some degeneration of the spino-cerebellar tracts, in the peduncles of the cerebellum, and in several tracts of the brain-stem, which cannot be regarded as efferent or "motor." Further, as Campbell himself rightly recognized, the cortical disease is not limited to the giant Betz cells, for there is also a "general cell-disturbance," and especially atrophy and disappearance of the supra-granular pyramids; the conclusion, therefore, he has tacitly drawn, that only the Betz cells give origin to pyramidal fibres, is manifestly unjustified.

Further arguments in support of his conclusion were obtained from the examination of brains of patients who died at long intervals after the amputation of parts of limbs. In these cases the chief cortical change was a condition of the giant-cells identical with the *reaction à distance*, and this despite the fact that the amputation to which it is attributed was in some of the cases of several years' duration. Similar changes had been previously described by Acquisto and Pusateri [1] and by Peli. The interpretation Campbell has placed on them may be questioned. In the first place, the problem arises: Are these chromatolytic changes to

be ascribed to a retrograde atrophy which oversteps the anterior cornual synapses, and thus involves the upper motor neurones? That this really occurs seems doubtful, as permanent atrophy of even the anterior horn-cells is far from constant after amputations. Further, the cytological changes Campbell describes are certainly not such as might be expected to result from this condition, and it is noteworthy that he could detect no diminution of the affected cells, though on his own showing the cell-changes must have existed for years. There is another possibility which Campbell himself seems to have considered in raising the question "whether, in the case of the cortical motor element, suppression of the discharge of energy which it elaborates, by division of the second link in the neuronic system," can "result in corporeal disintegration"; it is that the disturbance of the physiological equilibrium of the motor cortex which must result from the amputation of a limb may lead to structural change in its cells. If this be so, Campbell's conclusion as to the cells of origin of the pyramidal tracts receives little support of any value, for besides the fact that it is unsatisfactory to argue from the physiological to the anatomical, it cannot be maintained that changes resulting from such physiological inactivity will express themselves only on the cortico-spinal neurones; it seems more probable that the whole system of neurones concerned in the elaboration of the cortici-fugal discharges would be involved. In fact, Campbell invalidates his chief conclusion by the statement, "particular attention was not paid to the other cell-layers; and although we think that the large pyramidal cells had suffered a reduction in numerical strength, we cannot attach much importance to the observation, because we did not verify it by making careful enumerations and drawings."

IV.

The first question with which we have to deal is: *From what region of the cerebral cortex do the cortico-spinal tracts take origin?*

It must be at once pointed out that in the present communication we are concerned only with the actual cortico-spinal fibres—that is, those which form the upper motor tract for the volitional movements of the limbs and trunk—and that we cannot deal with the fibres which pass from the cortical centres for the movements of the eyes, or to the bulbar lower motor centres. This restriction has been necessary owing to the method on which we have relied, as on dividing the pyramidal tracts above the spinal cord other cortici-fugal fibres would be also injured, and

this would seriously complicate our task, and might invalidate our conclusions.

The region of the cerebral cortex from which, according to our observations, the fibres of the cortico-spinal tracts take origin, has been already mapped out in each of the brains we have examined; further reference is therefore necessary only to the exact topographical relation of this area in each class of animals to the more constant cerebral sulci.

In the macaque monkey it lay entirely in front of the fissure of Rolando and never extended to the posterior central gyrus, but the exact relation of its posterior margin to the floor of the sulcus was variable, as towards the apex of the hemisphere it practically coincided with it, but more laterally it gradually receded from the floor along the anterior wall of the fissure. A similar relation was observed in the chimpanzee.

In the two human brains we have used in this work the posterior limit of the area from which we have shown that the cortico-spinal fibres take origin never crossed the bottom of the sulcus, but in a few of the many hemispheres, normal and pathological, in which this region has been examined by one of us, the giant-cells from which we shall show that the cortico-spinal fibres spring extended behind the fissure, and in one case almost reached the apex of the posterior central gyrus. In fact, as Schäfer, Sherrington [26], Elliot Smith, Vogt [29], and Brodmann [5] have insisted, the relation of even the chief fissures to homologous cortical areas is by no means constant even in the same species, and their importance in cortical localization may be consequently overrated.

It is noteworthy that the region of the cerebral cortex that gives origin to the cortico-spinal fibres subserving the trunk and limbs in both the dog and cat lies chiefly behind the sulcus cruciatus, and does not extend lateral to the sulcus coronalis.

In the lemur none of the margins of the area can be accurately defined by the position of a sulcus.

There are very few anatomical observations known to us which help to confirm our conclusion that in the primates the cortico-spinal fibres spring only from the cortex in front of the sulcus centralis, though it may be seen from the extracts in our opening paragraphs that there is a tendency to the opinion that the major part of these bundles come from the anterior central gyrus.

Campbell's [7] work, and especially his arguments based on the cortical changes he found in amyotrophic lateral sclerosis and after

amputations, are extremely suggestive, but, as we have seen, his conclusions are open to serious criticism.

Mellus [19], however, failed to trace degenerated fibres into the spinal cord by the Marchi method in several macaque monkeys after the removal of Beevor and Horsley's "thumb centre" in the posterior central gyrus, and only in one animal could he demonstrate a few. Further, Grünbaum and Sherrington [14], working with the anthropoid apes, were unable to find any degeneration in the spinal cord after removal of portions of the cortex of the posterior central gyrus, though spinal degeneration was always obtained from lesions of the anterior central gyrus.

On the other hand, Vogt [29] found, besides extensive degeneration of the pyramidal tracts after destruction of the anterior central gyrus, very slight ("sehr geringfügige") pyramidal degeneration from lesions of the posterior central cortex; unhappily, a detailed description of his observations is not given. Von Monakow, too [20], from the investigation of secondary degeneration from cortical lesions, came to the conclusion that in man pyramidal fibres spring from the posterior central gyrus.

But evidently after cortical ablations a negative result is of much greater value than a positive; and it seems to us that a point of fundamental importance has been definitely settled in the present investigation carried out over a long series of animals, and in man by a method free from the fallacies which so easily arise in the use of the excitation method, which indeed have given such contradictory results in even the best hands, viz., that *the posterior central (ascending parietal) gyrus is in no way directly concerned with the origin of the motor (pyramidal) fibres subserving the limbs and trunk.*

V.

The second question with which we are concerned is: *From what cells of the cerebral cortex do the cortico-spinal fibres take origin?*

In all our material in which the cortico-spinal tracts had been destroyed by lesions so situated that no other cortici-fugal fibres could have been injured the reactionary cell-changes could be found only in the infra-granular layer of the cortex (Campbell's VI., Brodmann's V. layer); we never succeeded in detecting chromatolytic changes in the superficial pyramids, in the polymorphous layer, or in any of the smaller pyramids or granule cells. The infra-granular layer of the area of cortex to which we found the changes limited contains not only large pyramidal

cells which correspond approximately in size and shape to those which occupy this layer in other regions of the cortex, but also cells much larger, more bulky or pyriform in shape, more richly supplied with coarse masses of chromatophilic material, and possessing a nucleus which is small in proportion to the cell-body. These giant-cells, which were originally described by Betz, and later by Bevan Lewis and Clarke as the "ganglionic cells," are very variable in size; some, indeed, scarcely exceed in bulk those which we regard as ordinary large pyramidal cells, but from these they may be easily distinguished by their shape and staining reactions. It has been in these giant-cells, and in them only, that we have found changes when the cortico-spinal tracts alone of the cortici-fugal fibres were destroyed by the lesion. We must therefore conclude that it is from these cells, and from them alone, that the pyramidal tracts spring.

The question then naturally arises: Do these giant-cells which are limited to the region from which the pyramidal tracts arise give origin only to cortico-spinal fibres? It is difficult to give a definite answer to this, but it appears to us that the reply should be in the affirmative. After experimental section of one pyramidal tract in the higher cervical segments of the cord we always found, even after considerable periods, a certain proportion of the giant-cells of the opposite hemisphere remaining intact—in the callithrix monkey, for instance, about one-twelfth to one-fifteenth of the normal number. But this is what should be expected even if all the giant-cells do send their axis-cylinders to the spinal cord, as in all mammals a certain proportion of the cortico-spinal fibres run through the homo-lateral columns of the cord and consequently escape injury in a lesion of the opposite side. In this fact, too, we find the explanation of our observations that faradic unipolar stimulation of the affected cortical area of the left hemisphere in this monkey produced only movements of the limbs of the same side.

But this explanation of the escape of a certain number of the giant-cells in the hemisphere on the side opposite to the spinal lesion demands, if it be correct, that a certain proportion of those in the corresponding regions of the homo-lateral hemisphere, approximately equal to that remaining intact in the opposite, should be affected. And in fact we have found this to be the case in every one of the brains we examined within the two months after unilateral section of the spinal cord; it would be evidently scarcely possible to make this observation at the stage in which the only prominent change in the cortex was disappearance of the affected cells, as it was in one of our monkeys.

In our human *Case* 1, on the other hand, in which there was a complete transverse lesion of the spinal cord in the seventh cervical segment, scarcely a single normal giant-cell could be found in either paracentral lobule, or in the apical portion of the anterior central gyrus; that a certain proportion remained intact at the lower margin of the affected area on the lateral convexity and in the region of the cortical motor-centres for the finger and hand movements, may be explained partly by assuming a certain overlapping of the centres with normal and interrupted projection systems, and partly also from the fact that the plane of our sections was not exactly parallel to the lower margin of the affected area. On the other hand, the escape or slighter affection of some of the cells may have been possibly due to the existence of collaterals from their axis-cylinders to the corpus callosum or elsewhere, so that sufficient function was still possible to the cells to save them from degenerative changes.

From the above facts we may conclude that certainly almost all, if not all, the giant-cells of the portions of the precentral areas we have investigated send their axis-cylinders to their cortico-spinal tracts.

The published observations we can collect to corroborate this view are few, though it has been several times already brought forward, but without any unequivocal proof or even strong evidence in support of it. Cajal [6] indeed, who assumed that the pyramidal tracts spring from the large pyramidal cells of the fourth and sixth cortical layers, immediately adds, "but we must remark that this is only a more or less plausible hypothesis which is entirely without physiological and anatomo-pathological foundation."

According to von Monakow [20], "the pyramidal tracts take origin from the giant pyramidal elements (Riesenpyramidenkörpern) of the central convolutions"; but as has been already pointed out, the large superficial pyramidal cells are referred to here; indeed, it cannot be the giant- (Betz) cells alone, as these exist only in the anterior central gyrus. It appears to us that of the other authors, Marinesco alone had, in the cortical changes he observed secondary to spinal lesions, sufficient evidence for any definite statement as to the cells of origin of the cortico-spinal tracts.

The changes which develop in the precentral cortex secondary to capsular lesions, and those we found in the lemur after unilateral section of the crus, may be contrasted here with those which result from destruction of the cortico-spinal fibres alone. In the latter condition we found only the giant-cells affected, while after interruption of the

projection fibres from the cortex to the central ganglia and lower centres by capsular lesions or by section of the crus there occurs in addition chromatolysis, and later atrophy and disappearance, of many of the pyramidal cells of the supra- and infra-granular layers, but especially of the latter. Von Monakow also found the large pyramidal cells degenerated after capsular lesions, but it is not evident from the descriptions given by Marinesco, and by Ballet and Faure, whether they observed changes in these ordinary large pyramidal cells or only in the giant-cells.

It therefore appears that, in the central gyri at least, the ordinary large pyramidal cells, but especially those of the infra-granular layer, give origin to the shorter projection fibres of the cortex. And the giant-cells may be regarded as large pyramidal elements modified in the course of phylogenesis as the cerebral cortex acquires a direct connection with the spinal cord, and we consider from data obtained in the present research that *the infra-granular giant pyramidal cells undoubtedly give origin to the cortico-spinal fibres subserving the limbs and trunk, and in the cortical areas under consideration to these only.*

VI.

The question as to *whether the origin of the cortico-spinal tracts is co-extensive with the excitable cortical area subserving the limbs and trunk* is of great interest, but a satisfactory reply is rendered more than usually difficult by the fact that "the excitable motor cortex" is a very relative term, and the areas to which it has been applied have been mapped out strikingly differently by various observers; of this anyone can convince himself by a glance at Plate 4 of Vogt's [30] monograph, in which the results obtained by various experimenters on the cercopithecinæ are reproduced.

Evidently the extent of cortex from which movements can be obtained depends on several conditions, and even when minimal stimuli are employed the state of anæsthesia, the condition of the exposed brain, and factors which facilitate the spread or irradiation of the current both superficially and deeply can seriously influence the results. These complicating factors have made the term "motor cortex" very vague and indefinite.

From the anatomical point of view "the motor zone would be best and most sharply defined and delimited as the region of the pyramidal tracts" (v. Monakow), but anatomy has failed hitherto to delimit this

region accurately. We may, however, attempt to show how closely the areas we have mapped out by anatomical methods coincide with the "motor cortex" as defined by the more recent physiological investigations.

FIG. 9.

A reproduction of Vogt's figure showing the cortical centres for primary movement in the lateral surface of the hemisphere. The centres for the movements of the limbs and trunk are enclosed in front and below by the thick broken line.

In no other class, perhaps, have the excitable cortical centres been so frequently or so carefully studied as in the lower monkeys, especially in the macaque family, and in this class consequently we may begin our attempt to correlate our anatomical facts with physiological con-

clusions. For this purpose we select the work of C. and O. Vogt, who recently carried out experiments in a large number of animals with every possible precaution [30].

Fig. 9 is a reproduction of Vogt's composite diagram of the results obtained by unipolar faradic stimulation of the cortex in twenty-seven animals, the centres for the movements of the limbs and trunk being enclosed by a thick line. On comparing this with our fig. 4 obtained by an entirely different method the practical identity of the area of origin of the cortico-spinal fibres with this portion of the "excitable motor cortex" is very striking. The absence of excitable foci in the posterior central gyrus, and the close correspondence between the line in Vogt's diagram which separates the centres for the upper limb from those for the facial movements, with that of the lower limit we obtained for the area of origin of the cortico-spinal fibres, are worthy of note. The frontal margins of the two areas also correspond fairly closely, except perhaps that our area includes part of Vogt's "unerregbareres präcentrales Feld," that is, a small area lying above and in front of the superior precentral sulcus. On the other hand, Vogt places no excitable foci in the gyrus marginalis on the mesial surface of the hemisphere, while we have found that a not inconsiderable proportion of the cells of origin of the cortico-spinal tracts lie in this region. It must be, however, pointed out that Vogt's observations on the inexcitability of the mesial surface of the hemisphere are at variance with those obtained by many other investigators, especially Horsley and Schäfer; the German authors, it is true, obtained movements by stimulation of this region, but came to the conclusion that it is not an excitable area in the restricted significance of the term, as identical movements could be always obtained from the lateral surface of the hemisphere, and stronger currents were always needed than there; further, the movements obtained from the mesial surface were more variable and less localized than those from the convexity of the brain. Further physiological investigations may be awaited before any attempt is made to explain this discrepancy between the physiological "excitable cortex" and the region of origin of the cortico-spinal fibres in the gyrus marginalis. It is noteworthy that in the orang, C. and O. Vogt discovered true excitable foci on the mesial surface, as Sherrington and Grünbaum had previously done in the chimpanzee.

Records of stimulation experiments on the cerebral cortex of the lemur have been recently published by Völsch [31], O. and C. Vogt [30], and by Mott and Halliburton [21]; previous observations had been

made by Elliot Smith and Page May [27], and again by Elliot Smith and W. H. Wilson [28]. One of us (W. P. M.) has during the last three years made similar observations on six other lemurs, and these excitation experiments, which will be published in detail later, showed definitely that, as in the post-central gyrus of the monkeys and apes, no motor response could be produced by stimulation with a minimal strength of current behind the sulcus X, though when an electrode was placed in its depth movements, most frequently of the hip, could be obtained. In fact, the posterior limit of the excitable cortex coincides almost exactly with that of the area mapped out in fig. 3, not only on the lateral surface but on the mesial as well, and indeed the extent of each area is almost identical. These excitation results agree with those obtained by one of us in conjunction with Elliot Smith five years ago, and more recently by C. and O. Vogt, but the latter do not extend the area to the mesial surface of the hemisphere. On the other hand, Halliburton and Mott have mapped out the motor centres over a much more extensive area of cortex, especially posterior to sulcus X.

It may be pointed out that one lemur was the only animal in which the upper motor neurone fibres for the face, tongue and head movements were divided, and corresponding thereto we have in this animal alone found histological changes in the cortical centres for these movements.

The excitable "motor" cortex of the chimpanzee has been mapped out by Grünbaum and Sherrington [13] in their classical contributions which form a landmark in cerebral localization. The stimulation results obtained in our animal entirely confirm their conclusions, but with us the area, stimulation of which by minimal currents gave motor responses, extended slightly in front of the precentral sulcus; for instance, in the right hemisphere flexion of the wrist was obtained 4 to 5 mm. in front of it. In fact, the anterior limit of the excitable area, as defined by physiological methods in the right hemisphere, coincided exactly with the frontal margin of the area of origin of the pyramidal tracts, as delimited by anatomical methods in the left hemisphere.

The slight discrepancy which exists between our histological results and the physiological results of Grünbaum and Sherrington may be due to individual variation; in fact, these authors have insisted on the inconstancy of the sulci, and therefore on the fallacy of using them as strict landmarks. On the other hand, as Campbell has already pointed out, and we confirm the observation, the giant-cells become sparser towards the frontal margin of the area, and this region must therefore,

though part of the motor cortex, give a smaller response to the same strength of current than would be obtained more posteriorly. Grünbaum and Sherrington recognized this fact in their stimulation experiments, for they write that "the anterior limit of the motor field is not of a sharp, abrupt character, but fades off forwards somewhat gradually. This edge extends further forward under *Bahnumg.*" It is therefore evident that in the chimpanzee, too, the origin of the cortico-spinal tracts is closely co-extensive with the excitable "motor" cortex for the limbs and trunk.

It is useless to attempt to discuss in detail the topographical relation of the area of origin of the cortico-spinal tracts in man to the excitable motor cortex, as the latter naturally cannot be investigated by surgeons under such favourable conditions as in the lower animals. Yet a considerable number of observations, especially by Horsley, Cushing and Krause, have accumulated, from which it appears extremely probable that in man, as in the anthropoid apes, the motor centres lie entirely in front of the fissure of Rolando, and occupy only a relatively small area on the surface of the anterior central gyrus. This fact is in entire agreement with our anatomical observations.

In dealing with the carnivora we are also in difficulties owing to the want of recent and exact observations on the topography of the excitable cortical centres for the movements of the trunk and limbs in their brains. It is evident, however, on comparing Hitzig's descriptions and the diagrams of his stimulation results with our figures that the area from which we trace the origin of the cortico-spinal tracts is practically co-extensive with the cortical centres for the limb and trunk movements discovered by Hitzig.

Hence, from our own stimulation experiments on the animals described in the present paper and elsewhere, and by reference to some of the chief classical excitation investigations of others, we must conclude that *the origin of the cortico-spinal tracts as delimited by our method is co-extensive with the excitable cortical area for the limbs and trunk.*

VII.

Finally the question comes: *Does the area of the origin of the pyramidal tracts coincide with any structural type of the cerebral cortex?*

There is a special interest in this question, as within the last few years the whole of the cerebral cortex of man, as well as of representatives

of most of the mammalian classes, has been divided by several observers into a large number of areas, each characterized by its histological structure. The fullest communications on this subject we owe to Campbell [7], whose work was first presented to the Royal Society in 1903, and appeared in full in 1905, and to Brodmann [5], who has published a series of papers since 1903.

The importance of this sub-division of the cortex by histological methods lies in the fact that from difference in structure we may infer some difference in function, and a structural sub-division thus becomes parallel to a functional. This significance has been long recognized, indeed, in the early days of cerebral localization Bevan Lewis and Clarke discussed the relationship of definite areas characterized by the presence of "ganglionic cells" to the motor area as defined by Ferrier. Many other authors have applied the term "motor area" to the cortex of a certain region, or an area with certain structural peculiarities, only because some experiments had shown that movements could be obtained by excitation of it; and some, indeed, have been entirely dominated in anatomical investigations by more or less untrustworthy physiological data. Cajal [6], for instance, has included both central gyri in the "motor area," though recognizing the great difference there is between the structure of the cortex of each. The most noteworthy attempt to correlate function with structure has been made by Campbell, who has assigned specific functions to most of the cortical structural areas he has described. Brodmann has also recognized that it is a logical postulate that each area of specific histological structure has a specific function, but he, happily, has not burdened his observations with vague hypotheses regarding function. For it must be evident that the architecture of an area alone cannot be a trustworthy guide to its function; and that a physiological area should fall within or include a portion of a structural field is evidently no argument that this function is specifically related to that structural area, unless it can be definitely shown to be accurately co-extensive with it.

Excepting, perhaps, the calcarine type, with which the painstaking observations of Bolton have definitely associated the visuo-sensory function, the function of no structural area of the cerebral cortex has been made so probable as that which covers part of the anterior central gyrus in the primates. Campbell originally showed, in the brains of the apes that had been used by Grünbaum and Sherrington, that this structural area coincided very closely to that which responded to electrical stimulation. Vogt, on the other hand, has investigated the relation of the

excitable cortex to this structural area by numerous stimulation experiments in the monkeys and other animals, and found that though in the anterior central gyrus the excitable area lies within Brodmann's area giganto-pyramidalis the two areas are not exactly co-extensive. The centres in the frontal lobes from which movements of the eyes can be obtained, and the focus from which mastication movements may be produced, correspond to other structural areas.

But no more definite proof of the physiological value of the histological sub-division of the cerebral cortex could be brought than the demonstration by anatomical methods that the area giganto-pyramidalis is exactly co-extensive with the field of origin of the upper motor tracts. Our previous conclusions have practically done this as far as man, the ape and monkey are concerned, for on the one hand we have found that it is only from the giant-cells of the anterior central gyrus and the corresponding portion of the paracentral lobule that the cortico-spinal fibres spring, while on the other these same giant-cells determine the extent of a structural field, the precentral area of Campbell, or the area giganto-pyramidalis of Brodmann. This area, it is true, is more extensive than that from which we have shown that the cortico-spinal fibres take origin, but there can be little doubt that from the portion of it remaining over the analogous cortico-bulbar fibres arise.

With this reservation we may then conclude that the origin of the pyramidal tracts in man, the anthropoid apes, and the lower monkeys is co-extensive with a "structural field."

In the lemur the area of origin of the pyramidal tracts is approximately the same as the histological field delimited by Page May and Elliot Smith [27] and by Brodmann [5], but it differs considerably from the "motor area" mapped out by Mott and Miss Kelley [22], who have placed the greater part of it behind the sulcus X.

The region from which in the dog we have found that the cortico-spinal fibres take origin corresponds closely with part of the area delimited by Brodmann [5]; it has practically the same posterior limit, and includes very little of the anterior sigmoid gyrus. According to Campbell [7] and Köppen and Löwenstein [16], the greater portion of the anterior sigmoid gyrus is included in this area, but with this statement we can certainly not agree. On the other hand, we found no changes lateral to the sulcus coronalis, or in the anterior portion of the gyrus sigmoideus, though these regions contained intact giant-cells. But if, as appears probable from stimulation experiments, it is from these unaltered regions that the cortico-bulbar fibres arise we may conclude

that in the dog, too, the origin of the cortico-spinal fibres is co-extensive with part of a "structural field."

In the cat the area we have mapped out as the origin of the pyramidal tracts corresponds closely with the structural fields of Campbell and Brodmann.

Conclusions.

After division of the motor pyramidal fibres in the upper cervical region of the spinal cord there appears reactionary chromatolysis and atrophy of the cells in the cerebral cortex from which these fibres take origin. By operating thus on a series of animals (cat, dog, lemur, monkey and chimpanzee), and by utilizing two suitable cases in man, it has been possible to attain by histological methods the following conclusions:—

(1) The exact area of the cerebral cortex from which the cortico-spinal fibres subserving the limbs and trunk take origin is that shown in our figures and described in our text. In the primates this area lies entirely in front of the central (Rolandic) fissure.

(2) These cortico-spinal fibres arise only from the giant pyramidal cells of the infra-granular layer of this portion of the cortex, and these cells probably give origin only to cortico-spinal fibres.

(3) The area of origin of these cortico-spinal fibres coincides closely with the "excitable motor cortex" subserving the limbs and trunk, as this has been mapped out by recent investigations.

(4) This area of origin of the cortico-spinal fibres is co-extensive with part of a structurally differentiated cortical field.

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A NOTE UPON THE FARADIC STIMULATION OF THE POSTCENTRAL GYRUS IN CONSCIOUS PATIENTS.[1]

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ONE of the most important steps in our progress toward a more exact localization of function in the cerebral cortex was taken when, by a method of unipolar faradization, Sherrington and Grünbaum accurately delineated the confines of the so-called motor area. Their circumscription of this electrically excitable strip of cortex in the ape to the anterior wall of the fissura centralis (Rolandi) and to the adjoining surface of the precentral gyrus, has received confirmation through the more recent studies of myelinization, and through investigations into the finer histology of the cortex, which have shown that this area corresponds with the distribution of the Betz cells. Sherrington and Grünbaum's observations on the anthropoid brain, furthermore, have since been confirmed for man by Krause and Frazier; and I have had the occasion myself to stimulate the cortex of more than fifty anæsthetized patients with results in exact accord with those reported in 1901 from the Thompson Yates Laboratory of Physiology.

This surprising delimitation of what had previously been considered a wide territory to a relatively narrow precentral strip, left, without definitely proven function, the large portion of Munk's sensori-motor field—the old "motor area" of others—lying posterior to the central fissure. Conjectures have naturally arisen in regard to the function of this field—one from which motion may be elicited by undue strength of current—and the presumption that it is a sensory end-station has received support from certain histological studies (notably those of Alfred W. Campbell) as well as from a number of carefully observed clinical cases.[2]

[1] Presented at a meeting of the American Physiological Society, December 30, 1908.

[2] It would thus appear, as is so often the case with disputed points, that there is an element of truth on both sides; for the original "motor area," embracing the convolutions on each side of the central fissure, appears to be sensori-motor, though not in Munk's sense—namely, with coinciding or superimposed afferent and efferent stations.

There can be no doubt but that lesions of the gyrus precentralis can lead to motor disturbances without recognizable sensory loss; on the contrary, a lesion limited to the gyrus postcentralis will almost inevitably inhibit normal free movements. I have seen a number of

The experimental study of sensation in animals, being limited to the interpretation of reflex actions, is most difficult and unsatisfactory. Needless to say, it is a matter which requires on the part of the subject not only an analysis of his sensory impressions, but their transference by descriptive speech to the observer, who in turn must interpret this description; for at best it is difficult to find words precisely indicative of many forms of sensation.

Owing to the impossibility of this necessary communication the making of observations on the sensory cortex of unanæsthetized animals would be as futile as during a state of narcosis. This, however, is not the case with man.

A year ago I reported, with Dr. H. M. Thomas, a surgical experience[1] in which at a second-stage operation an osteoplastic flap, previously made, was re-elevated, the dura reflected, the cortex incised, and a subcortical cystic tumour removed from the postcentral field of an unanæsthetized patient. The procedure, with the exception of accidental dragging upon the dura, and the final reclosure of the scalp, not only occasioned no discomfort, but was attended on the part of the patient by a lively and helpful interest in the performance. He even informed us of a focal sensory attack which occurred early in the proceedings, evidently incited by the preliminary palpation of the exposed brain. At the first session of the operation, under anæsthesia, the motor cortex had been electrically delineated, and we greatly regretted that after safely concluding the second stage we had not taken the occasion to test with the faradic current the postcentral areas.[2]

instances of this. Thus, in a patient with a glioma of the postcentral gyrus, partial hemianæsthesia was accompanied by marked motor disturbances, but no degeneration of the pyramidal tract was demonstrable at autopsy; and, further, an operative case with prompt restoration of normal motility after the evacuation of a postcentral, subcortical clot in a patient presumed to be hemiplegic, has been detailed in my Carpenter Lecture for 1906 (*New York Medical Journal*, January 26, 1907).

On a few occasions, in cases of focal epilepsy, characterized by a definite sensory aura in face or hand, I have extirpated a segment of the postcentral convolution corresponding with the level of the precentral strip, from which movement in the part concerned was elicited by cortical stimulation at the time of operation. Occasionally, though not always, a certain degree of hyperæsthesia has subsequently been demonstrable in the expected field; but this has always been a transient affair, clearing up in large part rapidly just as does a motor palsy resulting from the extirpation of a small segment of the precentral gyrus.

These observations have never been such as to justify definite physiological conclusions, for the extirpated segment has usually been small—a cubic centimetre of tissue possibly—and the deeper cortex lining the wall of the fissure must often have remained intact.

[1] "Removal of a Subcortical Cystic Tumour at a Second-stage Operation without Anæsthesia," *Journal of the American Medical Association*, 1908, vol. i., p. 847.

[2] A footnote describing a single, and the first experience in this direction, accompanied the article referred to above. In making a subtemporal defect for purposes of decompression in a case of brain tumour—a procedure usually concluded under anæsthesia at one sitting—it was necessary, owing to some meningeal bleeding, not easily checked, to postpone the opening of the dura to a second session. This was accomplished without an anæsthetic, and the exposed temporal lobe was stimulated, giving the patient certain definite auditory impressions which he clearly distinguished from the "buzz" of the vibrator.

In the past year, however, the exigencies of two surgical cases have given us the looked-for opportunity of making further observations upon the sensory field. It is the purpose of this paper to record solely the physiological aspects of these observations, although their surgical aspects are possibly of even greater importance; for if it will be possible in the future to pick out with an electrode areas of the brain from which the sensory aura of a focal convulsion has originated, we shall have advanced a long way toward the possible operative localization of subcortical irritative lesions of the immediately postcentral field.

Case 1. *History.*—The patient, a sturdy and intelligent boy of 15 years of age, was referred by Dr. H. M. Thomas to the surgical service of the Johns Hopkins Hospital on June 16, 1908, suffering from "convulsive attacks originating in right hand and right side of face." At the time of onset, two years before admission, these seizures were limited to a subjective sensory disturbance, characterized at first by periods of numbness in the little finger of the right hand, and finally by what was described as a "funny feeling" in the arm—a "gone sensation."

These purely sensory attacks increased in frequency and severity, and finally were followed by a twitching of the little finger; then by contractions involving the whole arm, and more recently by an extension of the motor disturbances to the right side of the face.

Though he had never himself observed an involvement of the right leg, the more severe seizures which occurred after his admission to the hospital were accompanied by a definite convulsive movement in the lower extremity as well.

A typical attack, many of which were observed, was preceded for a period of possibly ten minutes by a feeling of weakness or "goneness" in the arm. This was followed by tingling, roughly confined to the ulnar cutaneous distribution of the hand; then the arm would suddenly flex and be drawn up above the head. At this stage of the seizure he could occasionally check further progress of the "march" by grasping the affected arm with the left hand, and by pushing it violently to his side. No loss of consciousness accompanied the attacks, and usually, though not always, he could be made to speak during them. They were attended by a sensation of apprehension, but never by one of pain.

In the most severe seizures he would be drawn to the floor by an arching of the body to the right, with convulsive movements of the right side; but even in these attacks he was never known completely to lose consciousness. A distinct though transient weakness in the arm with irregular ataxic movements usually followed the attacks.

Beyond the presence of an incipient choked disc (hyperæmic stage), and a slight disturbance of pain and temperature sense over the postaxial surface of the hand and forearm, the physical examination was practically negative.

With the presumption that some organic lesion, possibly a tumour of the postcentral territory, would be found, an exploration was advised.

Operation (first stage, June 16, 1908.)—An area of the left hemisphere, as shown in the accompanying sketch (fig. 1), was exposed by the usual osteoplastic craniotomy. The hemisphere was found under slightly increased tension, but no abnormality was apparent.

Owing to the characteristic configuration of the central fissure, the landmarks of the exposed part of the hemisphere were perfectly clear, but the situation of the precentral gyrus was further assured by unipolar stimulation which elicited the usual sharp movements in wrist, in elbow, in shoulder and in face. The only subcortical investigation at this time was limited to the explora-

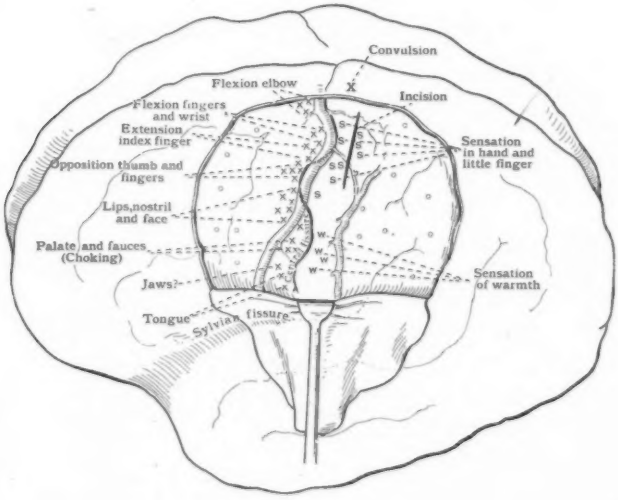

FIG. 1.

tory puncture of the postcentral gyrus in the vain hope that a cyst might thus be encountered. The wound was then reclosed.

The boy's distressing seizures continued unabated, until finally it was determined that some more radical attempt should be made to disclose, if possible, their source of origin. It was hoped that if the cortex could be stimulated while the patient was conscious; we might thus obtain some evidence of the situation of the presumed lesion sufficient to justify a more extensive subcortical exploration.

Operation (second stage, July 6, 1908).—After a preliminary injection of $\frac{1}{6}$ gr. of morphia, and under primary anæsthesia by chloroform, the edges of

the former incision were newly separated and the original bone-flap quickly re-elevated. The patient promptly regained complete consciousness, and while in this state, without occasioning discomfort, the dura was divided in the line of the previous closure, and the membrane was again reflected.

Cortical stimulation.—The following electrical observations were then made. The same movements as before were easily elicited with a mild faradic current from the precentral strip. These motor responses in detail and in the order in which they were obtained from the areas shown in the accompanying sketch (fig. 1) consisted of:—

(1) An opposing movement of thumb and fingers from points opposite to the unmistakable genu.

(2) Somewhat higher up, extension of the index finger.

(3) Still higher flexion of the fingers, which carried over to flexion of the wrist.

(4) At the upper margin of the exposed field, flexion of the elbow.

(5) Below the evident middle genu the movements, which required a somewhat stronger current, consisted of contraction of the side of the face.

(6) Movements of palate and fauces, a curious choking sensation being occasioned whenever they were obtained; and

(7) From the very lowest exposed part of the strip movements of the tongue occurred, and the patient experienced a sensation of movement in the lower jaw, though this was not certified by the observers.

It is to be noted that the subject was perfectly aware of these movements, and in the attempt to express the sense of feeling which was occasioned by them he said that it was the same sort of a drawing sensation appreciated when the muscles are "pulled" by peripheral stimulation—a familiar experience for him, owing to a long course of electrical treatment before his admission to the hospital. The movements, in other words, gave him the sensation of active muscular contraction alone.

Posterior to the central fissure, over an area roughly corresponding with the upper two-thirds of the exposed postcentral convolution (fig. 1), stimulation, with the same strength of current used to elicit the motor responses from the precentral gyrus, led to a sensation in the hand, arm and little finger—chiefly in the little finger—which was said to be exactly akin to the sensation that inaugurated his attacks. Stimulation lower down on the postcentral gyrus occasioned a sensation of warmth in the arm, but this was rather vague and indescribable.

It is to be noted that there were no painful sensations whatsoever, and further, that stimulation of the field in front of the motor strip and back of the postcentral convolution elicited no movements or sensations whatsoever, and the patient seemed to be unaware of the application of the electrode.

On elevating the upper edge of the dura at the point X (fig. 1) and placing the electrode there, an attack precisely similar to his usual attacks, inaugurated by the same sensory disturbances and followed by the customary abduction of the arm and arching of the body to the side, was produced. This lasted but

a few moments, and was not followed by a general convulsion nor by loss of consciousness.[1]

In the light of these observations, a number of small vessels crossing the postcentral gyrus were doubly ligated and an exploratory excision 3·5 cm. in length was then made between the ligatures (fig. 1) and carried down to a depth of about 2·5 cm., unfortunately without disclosing any lesion. The procedure was practically bloodless, and the edges of the incised pia-arachnoid were subsequently approximated with three delicate split silk sutures. No sensation whatsoever accompanied the making of this deep exploration.

The dura was reclosed, the bone-flap replaced, and under a second primary chloroform anæsthesia the scalp was quickly resutured.[2]

Case 2. *History.*—An intelligent man, aged 44, began to suffer in August, 1907, with attacks of Jacksonian epilepsy of obscure origin. These attacks, beginning in and often limited to the right hand, were trifling at first, but soon became more numerous and more severe. They were usually preceded by an uncomfortable numb feeling in the palm of the hand, associated with a sense of weakness. This definite aura would sometimes fade away without further progress, but more frequently would pass over into a motor attack. Often the definite motor seizures were inaugurated by a stinging sensation "like an electric shock," which would seem to run down between the little and ring fingers.

The earliest effect upon movement would be an uncontrollable extension, particularly of the ring and little fingers, with abduction of the latter. In attacks of a somewhat more severe type a "drawing" sensation would pass up the arm, accompanied by flexion of the elbow, abduction of the shoulder, and

[1] It is impossible to say whether or not stimulation of the postcentral convolution at its upper and mesial extremity, and possibly over on the mesial surface of the hemisphere, would have given sensory impressions in the lower extremity. No sensation occurred in the face from stimulation of the postcentral convolution at a level below the middle genu; but it is here again conceivable that the earlier excitation of the presumed sensory areas for hand may have led to their over-excitability, with the possible masking of a lesser sensation that may have occurred in the sensory area for face.

It may be noted that the mesial edge of the dural opening was 2 cm. from the mid-line; the exposed field measured 8½ cm. in width, and 7 cm. in a vertical direction.

[2] Though not essential to the main purpose of this report, the postoperative results of this cortical incision may deserve notice. It led to a slight sensory disturbance, limited to the ulnar side of the hand, little, and ring fingers. Tactual impressions over this area were dulled; there was a slight degree of hypalgesia, particularly at the tip of the little finger; and on the ulnar side of the forearm a temporary difficulty of distinguishing between heat and cold. There was subjective complaint also of the hands feeling tired. The steriognostic faculty was unaffected, but a loss of postural sense was demonstrable in the little finger.

The disturbance of afferent impressions was further evidenced by the slightly increased difficulty of performing finer movements, as in writing. The arm was a trifle stiff from an evident muscular hypertonicity, but muscular strength was unimpaired. Some incoordination in movement, increased during the closure of the eyes, was appreciable. All of these postoperative disturbances faded away in the course of a few weeks.

The surprising fact is to be noted that the cortical lesion occasioned sensory disturbances which appeared to be limited to the postaxial side of the arm, rather than in a distribution commonly supposed to characterize peripheral anæsthesias of cerebral origin—namely, of the "stocking" and "glove" type.

It is unnecessary to add that a possible extracranial source of origin for these sensory disturbances on the postaxial side of the limb, such as a cervical rib or other peripheral lesion, had been carefully eliminated.

tilting of the head to the right. During the seizures, even of this degree of severity, though confused and unable to respond when questioned, he would not lose consciousness. On a few occasions, however—six in all—a severe general convulsion has occurred, in which the inaugural sensory disturbance has passed down the side of the body before consciousness was lost.[1]

His history otherwise and the physical examination were practically negative.

Operation (first stage, December 8, 1908).—The patient took his anæsthetic badly, and, owing to the attendant cyanosis, an unusual amount of blood was lost while elevating the large osteoplastic flap. It consequently was deemed best to postpone further measures to a second sitting, in the hope that with the patient unanæsthetized the dura might be opened and the suspected lesion sought for by cortical stimulation in case its situation was not immediately apparent.

Operation (second stage, December 14, 1908).—After the administration of $\frac{1}{8}$ gr. of morphia and under primary anæsthesia from a few inhalations of chloroform, the original incision in the scalp was re-opened and the bone-flap re-elevated. The patient composedly and promptly recovered from the temporary narcotic effect of the drug. The dura was then opened in a line concentric with the incision in the scalp and bone and the membrane was reflected, no sensation of discomfort attending this procedure.

No abnormalities were evident on the surface of the exposed hemisphere, the topography of which was somewhat less clear than usual, owing to the presence of a large, single anastomotic vein (fig. 2), which was shown later, upon cortical stimulation, to overlie and thus obscure the greater part of an uncommonly straight Rolandic fissure.

Stimulation Observations.—Using a weak faradic current,[2] of one-half the strength that had been found necessary to elicit distinctive movements from the cortex of a recent case under anæsthesia, the convolution in the middle of the exposed field, just posterior to the aforementioned vein, was lightly touched for the briefest moment of time with the tip of the coiled platinum-wire electrode (Sherrington pattern).

The patient, who had been informed of our object and who was eager to assist in every way in his power, immediately responded, saying that he experienced a sensation which he located in the index finger of the right hand. On further questioning he said it felt "as though someone had touched or stroked the finger." (This and the following observations were corroborated from time to time by repetitions of the stimulus.) From points lower down on the same gyrus, a similar sensation of "touching" or "stroking" was experienced, but from this lower area the feeling was located on the back of the hand.

[1] A number of the minor attacks were observed and carefully described by Dr. H. M. Thomas, who had first seen the patient in consultation with Dr. J. M. T. Finney.

[2] The broad plate of the other pole in this, as in the former case, was applied to the thigh of the same side [left].

In order to be assured of the exact convolution from which these sensory responses occurred the gyrus lying anterior to the large vein was then touched about in the middle of the exposed field and opposite to what appeared to be a possible middle genu; a prompt flexion of the thumb into the palm of the hand followed this stimulus. The movement was unaccompanied by any sensation other than that of change of position of the thumb, which the patient promptly appreciated and described. In other words, there seemed to be no associated cutaneous sensation.

This latter observation was sufficient to certify the position of the fissura centralis (Rolandi), and although no further points on the precentral gyrus were subsequently stimulated, this same movement of the thumb was elicited as a control several times during the course of the later observations.

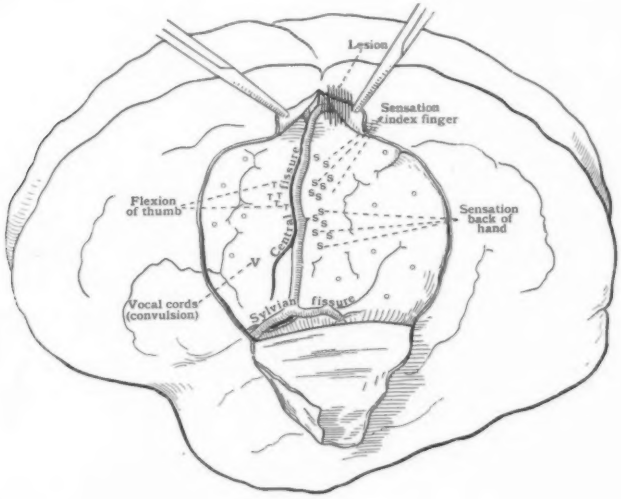

FIG. 2.

The precentral and postcentral gyri having thus been identified, the outlying convolutions were "coursed" in order to see whether any subjective sensations occurred from stimulation of other than the postcentral gyrus from which the sensory impressions had first been obtained. Thus the crests of all of the exposed convolutions, at about the points marked by small circles in the sketch (fig. 2), were stimulated, with the elicitation of no sensory and, needless to say, of no motor responses whatever. Occasionally, in order to be sure that the current was sufficient for reaction, the primary stimulation of the area giving sensation of the index finger and of that giving movement of the thumb was repeated.

In coursing the exposed portion of the hemisphere as described, the operator

finally touched the point V, which immediately led to a curious, long-drawn, hoarse inspiratory sound, evidently due to closure of the glottis; this was followed by a general convulsion, the first observable evidence of which was a drawing-down of the right platysma and corner of the mouth, with depression of the chin and separation of the lips.[1]

Apprehensive lest a possible repetition of this unexpected convulsion might occur, and, from cyanosis and protrusion of the exposed cortex, occasion some damage, the operator desisted from further stimulation, although the exact area which occasioned the inaugural sensation of the patient's seizures had not been located.

At this juncture the administration of chloroform was resumed, and, under the anæsthetic, the upper and mesial edge of the postcentral convolution was more fully exposed by ronguering away a further portion of the skull at the upper edge of the cranial opening. This permitted an upward enlargement of the dural opening, as shown in fig. 2, and a lesion of the postcentral convolution, which was thought to be irremovable, was thus brought into view.

Comment.

These observations seemingly add confirmation to the view which ascribes a sensory function to the gyrus centralis posterior, but beyond this I shall make no endeavour to interpret their significance. Just what relation the afferent impulse bears to a motor response; just how stimulation of this supposedly sensory field is interpreted by the subject as sensory; why the motor response from stimulation of the gyrus centralis anterior occurs without any primary afferent impression, but only with the secondary consciousness of the movement—these and many other questions that arise are matters rather for the psychologist.

It is, perhaps, noteworthy that the sensations which were obtained were limited entirely to the hand and arm; and whether this means that there is an especially wide cortical representation for afferent impulses from this region, or whether these patients, owing to the characteristics of their seizures, possessed sensory centres from hand and arm which were unduly excitable, is difficult to tell, and will need further elucidation.

It is noticeable, in the last case, that the lesion which occasioned the

[1] It has seemed to me probable, from other experiences in the past, that the cortex in cases of epilepsy is more excitable than the cortex of non-epileptics; in the former it is traditionally easy, in fact, to occasion, even under anæsthesia, a Jacksonian fit which may run into a general convulsion. No apprehension, however, of this possible consequence of stimulation was felt in this particular patient, as such a weak current was being used. The numerous, rapidly executed and repeated stimulations of the seemingly non-excitable areas of the hemisphere may possibly have had an accumulative effect, so that when again approaching the lower part of the precentral convolution (Horsley's vocal-cord centre) the response to the stimulus was much more pronounced than was anticipated or was desirable.

seizures was found to lie higher on the postcentral gyrus than the areas which had been stimulated, so that presumably responses from the hand would have been brought about by stimulation there, just as they had been from a lower level of the convolution. It is possible, too, that the patient's attention in each case may have been so concentrated upon the affected hand that sensory impressions arising from leg, body and face passed unobserved. The fact that the sensations in the first case were precisely the same as those characterizing the aura of the patients' seizures would lend support to this view; but it was otherwise with the second case, for in this patient, though sensations occurred in the hand, they were other than those characterizing the inaugural stage of the fit and occurred over different skin fields.

Summary.

Two patients, afflicted with epileptic attacks inaugurated in each instance by a sensory aura in the right hand, offered unusual opportunities, as related, for cortical stimulation while in a conscious state during a "second-stage" operation.

In both of them the situation of the central fissure was determined by obtaining characteristic motor responses from the precentral gyrus, these motor responses being attended by no sensation other than that of the forced change of position which accompanies similar movements elicited by stimulation of a peripheral nerve.

On the other hand, in both of these patients stimulation of the postcentral convolution gave definite sensory impressions which were likened in one case to a sensation of numbness, and in the other to definite tactual impulses.

In both of the patients, furthermore, stimulation of the outlying convolutions gave no response whatsoever, either of a subjective sensation or of active movement.

ON CERTAIN CASES OF ACUTE TREMOR OCCURRING IN CHILDREN.

BY REGINALD MILLER, M.D.LOND., M.R.C.P.

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HAVING no pathological evidence to bring forward as to the nature of these cases, they have been described in the title in strictly clinical terms, the phrase "acute tremor" being used for the sake of brevity and to enforce the analogy between this condition and that named by Leyden "acute ataxia" (now attributed to encephalitis cerebelli). This latter consideration is not unimportant; for I believe, for reasons to be given later, that the cases here detailed are examples of encephalitis of the mid-brain and its connections.

The tremor which, with its acute onset, is characteristic of these cases, corresponds exactly with that described by Gordon Holmes (2) as associated with destructive lesions occurring in the cerebello-rubro-spinal system. It is a slow, regular tremor which at its worst is continuous except during sleep, although increased by voluntary movement, and which when less severe shows itself only on voluntary movement, or during periods of excitement. It may be universal in the head, tongue, and muscles of the trunk, abdomen, and limbs, and it is sometimes more definite in the proximal than in the peripheral parts of the extremities. In some of these cases the appearance of the child is very like that of one shivering all over from cold. In rate, the tremor is about five oscillations per second. Combined with the tremor is hypertonus, giving to the limbs some degree of uselessness, and rendering their movement slow, stiff, awkward, and this in the absence of true spasticity. There is little or no loss of power. In addition, there may be other signs present from the involvement of the parts of the brain in the immediate neighbourhood of the cerebello-rubro-spinal system, or from the presence of other foci of disease elsewhere in the central nervous system.

The important points, therefore, in these cases are three in number, the acute onset, the tremor and the hypertonus, the last two differentiating the condition from cerebellar encephalitis in which ataxia and

hypotonus are found, with the possible additions of nystagmus and scanning speech.

Where these cases have been reported, as by Batten [2], they have been grouped as cases of cerebellar encephalitis, but it would appear that they warrant separation from these, a view which I put forward in a paper concerning encephalitis [3], and which is also held by Poynton [4] in a communication in which two such cases are described, one of which is Case 3 of this series.

The cerebello-rubro-spinal system consists of two parts—the cerebello-rubral and the rubro-spinal. In the former the dentate nucleus of the cerebellum is connected with the red nucleus and optic thalamus of the opposite side by the superior cerebellar peduncle; in the latter the red nucleus is connected by the tractus rubro-spinalis (Monakow's bundle) with the opposite side of the spinal cord. In the pons Monakow's bundle passes close to the nucleus of origin of the seventh cranial nerve. In this system, therefore, are two decussations, each of which occurs in the immediate neighbourhood of the red nucleus, the superior cerebellar peduncles crossing before entering the nucleus, and Monakow's bundles crossing after leaving it. From this it follows that if the tremor be due to destruction of any part of the system, the movement will be on the same side as the lesion, unless the red nucleus itself or its immediate surroundings be involved, in which case it will be on the opposite side.

It will be convenient now to give an account of the clinical histories of the cases, but before doing so I must express my indebtedness to Dr. Voelcker, Dr. Colman, and Dr. Poynton for permission to use the patients I watched when Medical Registrar to the Hospital for Sick Children, Great Ormond Street. My thanks are also due to the Casualty Medical Officer of that hospital, Dr. L. G. Parsons, for his kindness in allowing me to see the last patient here reported, which was brought up to his department.

Case 1.

G. A. P., a boy, aged 2½.

History of illness.—In the first week of October, 1906, the child, when seated at table, was noticed to go suddenly "all of a heap," with his mouth drawn to the left. He was unconscious, and remained so for three weeks, although he was very irritable when disturbed. His limbs were observed to tremble. After three weeks he regained consciousness and was found to have lost his speech. He lay helpless in bed, with the shaking movements continuing all the time except during sleep. He was admitted to the Hospital for Sick Children, under Dr. Colman, on November 12, 1906.

Past history.—Had always been a very healthy child, and had learned to walk and talk well.

Family history.—The patient was the elder of two children; the other is well. The mother had no miscarriages and there was nothing of importance in the family history.

On admission (November 12).—The child was very well nourished, showing only slight bony signs of rickets. Apart from the nervous system no abnormalities were present.

Mentally the child was very irritable, although probably not in pain, and was extremely emotional. He cried very loudly, and would change from this into laughter, which was excessive and hysterical, resembling that of a child being tickled. He made no intelligible efforts to speak, but appreciated noises and things to eat. No diminution of emotional expression could be detected.

Tremor was seen in the head, tongue, trunk, and all four limbs. It was present except during sleep, but it was increased on voluntary movement. In the limbs it was more marked in the proximal than in the distal parts. In the hands it was a slow rhythmic tremor of about five per second. The whole appearance of the child was like one shivering from cold. In addition the voluntary movement of the limbs was performed slowly and stiffly as in a case of paralysis agitans. On the right side there was possibly some spastic rigidity.

Examination of the cranial nerves showed that there was some affection of the sixth and seventh nerves on the right side. The others appeared normal. The optic discs and the tympanic membranes were normal.

The reflexes showed little change. The right abdominal reflexes were absent, the left being just obtainable. The pupil, corneal and palate reflexes were normal. The tendon reflexes were brisk and equal on the two sides, and the plantar responses flexor. The jaw-jerk was active. There was reflex incontinence of urine.

Course of disease.—The child was seen at intervals for eighteen months. During the first weeks the evening temperature was slightly raised, as is seen in recent cases of acute poliomyelitis. A month after admission the cranial nerves and the abdominal reflexes had become normal and the tremor less marked, so that it was present only on voluntary movement. The hypertonus was still evident. A month later he was able to walk a little.

During the rest of the time slight further improvement took place. By March, 1908, all signs of the tremor had disappeared, but the movements of the limbs and of the head were slow and stiff. He was able to walk very fairly well by this time. Mentally he had made practically no improvement at all. He was a little quieter, but quite idiotic. He still laughed and cried hysterically, was extremely greedy, dirty in his habits, and made no intelligible effort to talk.

In February, 1908, he had three generalized convulsions which were not followed by any observable deterioration. In May, eighteen months after the

onset of the illness, he had a severe fit which proved fatal. No *post-mortem* examination was possible.

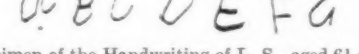
Localization.—From the affection of the sixth and seventh nerves on the right side, the general tremor and great emotionalism, we may surmise that the lesion was an extensive one involving the mid-brain and pons. But in addition it may well be that the cerebral cortex sustained some damage, which view may be supported by the prolonged unconsciousness at the time of the onset, the profound mental change, and the later development of epilepsy.

(This patient was shown by the writer as a case of encephalitis, chiefly affecting the mid-brain, at the Clinical Society, April, 1907.)

CASE 2.

L. S., a girl, aged 5¼.

History of illness.—On August 3, 1907 she complained of pains in the back and limbs and could not put the heel of the left foot to the ground. On the next day "shivering" of the right hand was noticed and she was unable to walk. She had no apparent feverishness, no convulsions, but talked in her sleep at night and seemed drowsy. She was kept in bed for a week. Only slight improvement was made until she was admitted to the Hospital for Sick Children on August 20, under the care of Dr. Colman.



A Specimen of the Handwriting of L. S., aged 6½ years, 16 months after onset of illness (Case 2).

Past history.—Had always been a big, strong child. Had measles five months ago and whooping-cough previously.

Family history.—Only child; the mother had had no miscarriages. Both paternal grandparents died of consumption. Maternal grandmother and uncle died insane at the ages of 62 and 29 years respectively. Parents healthy.

On admission (August 20, 1907).—The child was well developed and nourished. She was irritable and cried when disturbed; her memory and speech were good. When sitting up the head tended to assume the cerebellar attitude, the right ear approximating to the right shoulder and the face turning to the left with the chin raised. There was slight lateral nystagmus to right and left, none vertically. The gait was very ataxic and the child could not walk alone, falling backwards. The left limbs showed ataxic movements in both arm and leg. On the right side there was no ataxia, but tremor and hypertonus, the tremor being of the intention type and the voluntary movements of the limbs being slow and stiff. The cranial nerves were normal and the deep reflexes brisk, but rather less so in the left than in the right limbs. There was no evidence of involvement of either pyramidal tract.

Course of illness.—Very rapid improvement took place. The child quickly

became docile and quiet. Within a week the ataxy and the tremor diminished considerably, and within a fortnight she could walk unaided. A month later she could walk and run well, but some little ataxia showed itself in the left leg when she tried to kick a ball on the ground with the left foot. By this time the tremor had quite gone from the right leg, but was still just recognizable in the right hand.

In December, 1908, sixteen months after the onset of the illness, the child still showed a very slight tremor in the right hand when trying to do any fine action with her arm unsupported, but she was able to feed herself perfectly well. A specimen of her handwriting at this date shows how very slight was the tremor with her arm supported. The movement is at its worst when she is wakened from sleep, or when she is nervous. Mentally she was perfectly normal, and she appeared very strong and healthy in every other respect.

Localization.—From the presence of the ataxia on the left side, the cerebellar tilt of the head and the slight nystagmus, it may be supposed that the lesion was in the cerebellum, and that the tremor on the right side was due to the involvement of the right dentate nucleus.

Case 3.

A. C., a girl, aged 13 *months.*

History of illness.—The mother stated that the child had been seized with convulsions five weeks previously (*i.e.*, the beginning of August, 1908), and that these had continued occurring several times a day. After four weeks the child seemed slightly better for two days, but then relapsed, being convulsed and unconscious. Something wrong with the eye had been noticed for the last month. There had been no gastro-intestinal disturbance.

The mother was an Italian and could speak but little English, and I think that the history given may be correctly interpreted thus: that the child was seized suddenly with an illness in which movements of the limbs were present, and that for the first week the child was unconscious or very drowsy, and as this condition passed off the squint was noticed for the first time. This view of the history is supported by the fact that the child when first seen was neither convulsed nor unconscious, as the mother had stated. She was admitted to Dr. Voelcker's ward at the Hospital for Sick Children, under the care of Dr. Poynton.

Past and family history.—Nothing was noted on these points except that the parents had had no fits.

On admission (September 7, 1908).—The patient was a very fat child, showing rickety changes of the head and chest. She was conscious and was not irritable. The pupils were small, reacted poorly to light, especially on the right side, but dilated well under atropine. There was complete paralysis of the right external rectus, and there was definite weakness of the right side of the face, the eye not closing completely on this side. There was some doubtful weakness of the left external rectus.

The tremor was constantly present, except during sleep, in the head, trunk and limbs, being most definite in the lower extremities and least definite in the head. It was increased by voluntary movement and was in every other way similar to the rhythmic movements described in the other cases. It was very difficult to say that there was any definite hypertonus of the limbs. There was no loss of motor power. The reflexes were unaltered; the abdominal reflexes were all present, the knee-jerks brisk and equal, and there was no ankle-clonus. On attempting to elicit the plantar responses, voluntary movements of flexion were obtained. Lumbar puncture was performed on September 9, and clear fluid was obtained, which was sterile and showed no deposit or clot, and in which no cells or organisms were found.

Course of illness.—During the next week there was a good deal of improvement, the tremor becoming less and showing only on voluntary movement.

Localization.—From the affection of the sixth and seventh cranial nerves on the right side, the lesion, or part of it, may be thought to be pontine.

Case 4.

D. K., a girl, aged $2\frac{3}{4}$.

History of illness.—On October 24, 1908, the child suddenly became very drowsy and passed rapidly into an unconscious condition. There was no convulsion. She remained unconscious for four days. The tongue was noticed to tremble from the first day of the disease, but no tremor was seen in the limbs until the child sat up towards the end of the first week, when it was observed in the head and left limbs when voluntary action was undertaken. The movement was described as giving an appearance of "shivering." The squint and facial weakness were not noted. Rapid improvement had occurred. She had become greedy and was very noisy at night. During the last week she has begun to try to talk again.

Past history.—Physically well, but was described as being backward in her talking and always passionate and "spoilt." Habits not clean. Was said to have had convulsions at birth and at 6 weeks of age; no fits since then.

November 10, 1908.—Was seen as an out-patient at Paddington Green Children's Hospital seventeen days after the onset of the illness. She was found to be a strong, well-developed child. She was extremely passionate and irritable, and cried very loudly under examination; but there was no hysterical laughter, as in Case 1. There was weakness of the left external rectus and of the left facial muscles, the eyelids not being well closed on this side. Slight tremor was seen in the tongue, in the left arm and leg. In the limbs it was only present during volitional movement. Owing to the tremor in the legs she could not stand, but there was no actual loss of motor power in the limbs. The voluntary movements of the affected limbs were slowly and stiffly performed. So far as could be made out, the reflexes were unaltered; it was impossible to test the abdominal reflexes owing to the child's behaviour.

Course of illness.—When seen a fortnight later she was much more docile.

The cranial nerves and the left arm were normal, but the left leg showed slight tremor still, although she was beginning to walk alone. The abdominal reflexes were normal.

Within six weeks of the onset of the disease the child appeared to be perfectly well, walking, sleeping, and behaving well. She was said to be using more words than before her illness.

Localization.—It is probable that in this case there was a small lesion involving the sixth and seventh cranial nerves and the rubro-spinal (Monakow's) tract in the left side of the pons.

Case 5.

W. W., a boy, aged $1\frac{3}{4}$.

History of illness.—At the end of July, 1908, he suddenly began to scream violently, and appeared frightened, holding on to a chair. He was pacified after a few minutes, and as he got very drowsy he was put to bed. The next day continuous trembling was noticed in all the limbs. From this time he was unable to walk, he lost the few words he had learned, and became very noisy, nervous, and greedy. The trembling continued, but became gradually less.

Past history.—Was a strong child, good tempered, able to walk, and was beginning to talk before his illness. No other diseases.

Family history.—The child's mother had always been very nervous and "hysterical," and had lately developed epilepsy. She had had no miscarriages. Father strong. One other child, aged 8, well.

November 23, 1908.—When first seen, four months after the onset of the disease, he was found to be a strongly-built child, and very fat. He was very noisy, crying and laughing hysterically. He could not talk at all, and was mentally deficient and greedy. The tremor was seen in the limbs, showing only on voluntary movement; in the legs it was sufficient to prevent his standing. The movement of the limbs was slow and stiff in character. There was some jerky movement of the head and eyes, but no tremor or nystagmus. The cranial nerves and the reflexes were normal.

Course of illness.—A fortnight later he was a little quieter in his behaviour; the tremor was less, and the child was beginning to stand with assistance. There was no mental improvement. There had been no fits.

Localization.—Part of the lesion may be supposed to be in the mid-brain, involving the red nuclei.

Case 6.

A. Q., a boy, aged 15 *months.*

History of illness.—On October 19, 1908, the boy was put to bed well, and, although he slept with his mother, nothing was noticed until the morning, when he was found to be very drowsy and to be "shivering" all over, but the limbs were not paralysed. No fits were seen, nor was the boy unconscious. The movements very rapidly got better, but the child was not able to walk for about a

fortnight on account of the trembling of the legs. A week after the onset of the illness the right arm became useless, and hung down by the side. This paralysis was not accompanied by any constitutional symptoms, and was first noticed one morning after the child had had a normal night's rest.

Past history.—Had always been a fairly strong child, but was subject to attacks of vomiting. Had no previous illnesses except these bilious attacks.

Family history.—Only child. No neuropathic inheritance could be traced. No cases of infantile paralysis were known of in the neighbourhood.

January 29, 1909.—When first seen he was found to be a strong, fat boy, showing no trace of the tremor described by the mother. He was able to walk well, and could say more words than before the illness. No mental impairment could be found. The right arm was paralysed, and hung flaccid at the shoulder. There was slight power in the fingers of the right hand. According to the mother's statement, practically no improvement had taken place in the condition of this arm.

Localization.—It would appear that a slight lesion had occurred somewhere in the cerebello-rubro-spinal system, and that there had been a relapse a week later (the usual time for a relapse when such does occur), affecting the cervical enlargement of the cord.

Etiology.

It is necessary here to submit the clinical evidence which supports the contention that we are dealing with cases of encephalitis, using that term as indicating a disease of the brain similar to that which is known as acute poliomyelitis when it affects the spinal cord. In Case 6 we have a spinal lesion of the acute poliomyelitis type, occurring as a relapse in a child who had developed tremor a week previously. But apart from such evidence as this, acute poliomyelitis has certain well-marked characteristics which should be reproduced in polio-encephalitis with some modification, and these points may now be considered.

(*a*) The child who is attacked by poliomyelitis is very frequently the strong and fat, the delicate and thin children being notably spared. This rule held good in the six cases here reported, as it has in all other cases of encephalitis that I have seen. (*b*) The seasonal incidence of these cases corresponds to that of acute poliomyelitis, one being in July, two in August, and three in October. (*c*) The age-incidence, from 13 months to $5\frac{1}{2}$ years, corresponds exactly to that at which the spinal disease is commonest. (*d*) The amount of constitutional disturbance at the onset of the disease is very variable, as in poliomyelitis, although it is natural to suppose that convulsions and unconsciousness are likely to be of more common occurrence. In Case 1 the child was taken ill with a convulsion and was said to have been unconscious for the

following three weeks, while in Case 2 there was no fit and only slight drowsiness was observed. (*e*) In poliomyelitis the onset is acute and the harm done reaches a maximum within a few hours; anything like weakness becoming gradually an absolute paralysis is not seen. So, too, in these cases the disease is acute and its effects complete and absolute; but here care must be taken in examining the clinical history of the illness, for the same difficulty is experienced as has been found in dealing with cases of cerebellar encephalitis. Should the child be drowsy or unconscious the tremor may not be seen or may be regarded as signifying a convulsion, so that one may hear that the trembling came on some days after the onset of the illness. This possibility is well instanced in Case 4, in which the mother stated that the child was unconscious for four days and when sat up was seen to have shaking of the limbs. With questioning, however, it transpired that the tongue was seen to tremble when the child was fed on the first day of the illness. (*f*) As in poliomyelitis, the tendency of the disease is towards improvement or total recovery, while relapses are very exceptional. (*g*) Examination of the cerebro-spinal fluid was negative in the one case in which it was undertaken (Case 3), as it is in spinal cases.

In none of the cases here reported had the disease been preceded by one of the acute specific fevers of childhood within three months of the date of onset, a point which has been noted before in dealing with encephalitis and which by some has been used as an argument against the condition being the same disease as poliomyelitis. In my experience such a sequence in true cases of acute poliomyelitis is by no means so common as some have seemed to imply.[1]

It may be pointed out, without comment, that in the five cases in which it was possible to get a true family history two showed a strong neuropathic taint, while the third child was described as spoilt and passionate and suffered from nocturnal enuresis. I do not think that any such association has been noted in cases of acute poliomyelitis.

Symptomatology.

The acute onset, the tremor and hypertonus are the important characteristics of this group of cases, and have been sufficiently described above.

[1] In order to substantiate this point I have examined the records of the Hospital for Sick Children for cases of acute poliomyelitis whose onset occurred in 1906. Of these I found fifteen, and in only one was there a history of an acute specific fever within three months of the paralysis, while eight had never had any of the exanthemata at any time. The monthly incidence of these cases was August 5, September 6, October 3, November 1.

In addition, there may be other signs due to involvement of some part of the nervous system other than the cerebello-rubro-spinal tracts. Thus the anterior horn-cells of the spinal cord may be affected (Case 6), or the cerebellar involvement may produce ataxia (Case 2), or the sixth and seventh cranial nerves in the pons may be damaged (Cases 1, 3, and 4). Excessive emotionalism was present in Case 1, and to a less extent in Cases 4 and 5, and may perhaps be regarded as being produced by damage of the optic thalamus. Mental deterioration (Cases 1 and 5) appears to be a serious symptom, and if present may perhaps be thought to be due to an associated polio-encephalitis superior, involving the frontal areas of the cerebrum as has been described by Batten [1]. Hemiplegia may occur, with the tremor displayed on the paralysed side, or a third nerve paralysis.

Diagnosis.

This naturally falls under two headings: the character of the lesion and its localization.

It is not maintained that all cases of acute tremor are to be regarded as due to polio-encephalitis, but only that certain of them may be placed in this group. The diagnosis can to a large extent be made by the exclusion of other possibilities, but those etiological factors already mentioned—the type and age of child, the season of the year, the character of the onset, and the course of the disease—may be of use in settling the matter. The cerebro-spinal fluid shows no abnormalities. The most likely causes, apart from polio-encephalitis, are a tuberculous tumour or a thrombosis due to syphilitic endarteritis.

Of the former I have seen one example, the tremor being seen during the first few days in a case of tuberculous meningitis, and being due to a small mass found after death in the dentate body of the cerebellum. In such a case the child, although it may recover, is generally far from well nourished and robust; there may be signs of tuberculosis elsewhere, optic neuritis may be present, and the cerebro-spinal fluid will show an excess of lymphocytes. I have seen no case in which the tremor could be said to be due to a syphilitic thrombosis; but judging by what occurs where other parts of the brain are affected, the diagnosis should be clear by the presence of signs of inherited syphilis (particularly in the eye-grounds), and the possible warning convulsions or "fainting attacks." Here, again, lymphocytes would be present in the cerebro-spinal fluid.

The localization of the lesion has been discussed. The tremor and

hypertonus distinguish these cases from the true cerebellar ones which show ataxia and hypotonus. The part of the cerebello-rubro-spinal system attacked is diagnosed by the accompanying signs if such are present.

Prognosis.

There is a general tendency towards improvement. In all six cases the tremor rapidly diminished, and in a few weeks or months became inappreciable. Similarly the cranial nerve paralyses disappeared. Of far more serious import is the mental deficiency, which may remain after the acute attack is over, and which, where it was present in these cases, remained unimproved. In one of these epilepsy developed and proved fatal.

References.

[1] Batten. "Cerebral Symptoms due to Encephalitis," *Med. Soc. Trans.*, vol. xxvii., p. 116.
[2] Holmes. "On Certain Tremors in Organic Cerebral Lesions," *Brain*, 1904, p. 327.
[3] Miller. "On Acute Poliomyelitis and the Allied Conditions in the Brain," *St. Mary's Hosp. Gaz.*, December, 1907.
[4] Poynton. "Some Unusual Sequelæ of Convulsive Seizures in Childhood," *Lancet*, October 31, 1908.

A CLINICAL STUDY OF OPTIC NEURITIS IN ITS RELATIONSHIP TO INTRACRANIAL TUMOURS.

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CHAPTER I.

Introductory.

THIS paper is based entirely on the clinical records of patients admitted to the National Hospital between the years 1900 and 1907. It includes the cases of cerebral tumour admitted to the hospital during those years in which the diagnosis was confirmed either by *post mortem* or by the operative removal of the tumour. The work of summarizing these records was suggested to me by Mr. Marcus Gunn, and I have to thank him and the staff of the National Hospital for the ready permission that they granted me to utilize their most valuable records. I have specially to thank Mr. Gunn for his constant kindly encouragement and advice during the somewhat tedious task of abstracting and summarizing about 400 cases in all. Much of the value of the paper depends on the fulness and accuracy of his notes of ophthalmoscopic observations made from week to week on his visits to the hospital. Many of these patients I saw along with Mr. Gunn and was able to watch from day to day; for the ophthalmoscopic notes in some cases admitted while he was on his holidays I alone am responsible.

The worth of any statistical paper must rest to an equal extent on the care taken in making the original observations and on the method in which the statistics are used. In certain portions only of this paper are the numbers sufficiently large to justify the use of percentage values. If, for the sake of completeness, I have given percentages in other places where the numbers are smaller, I have been careful at the same time to give the actual numbers. And I hope that, apart from any value the paper may have in itself, it will be of use to some future worker seeking to collect a very much larger number of cases from the literature of this subject.

The value of any conclusions I have formed will vary proportionately to the number of cases on which they are based. At best, any clinical statistical paper is of utility only in suggesting hypotheses on which to base experimental or histological research, and I hope that certain lines of work which this paper indicates may prove productive of more definite results, either in my own hands or in those of some other worker in the same field.

The classification of tumours as belonging to different regions of the brain has been a matter of some difficulty, and must be, to a certain extent, arbitrary. I have endeavoured, as far as possible, to classify each tumour in the region to which it most properly belongs. But tumours frequently stray outside the boundaries by which we separate different cerebral lobes from one another. The greatest difficulty in this respect has been with the class of tumours which are generally known as subcortical. Cortical tumours are not restricted to the cortex alone any more than deep or subcortical tumours remain confined to the underlying white matter of the brain. Many of these latter, on the one hand, invade the overlying cortex, or, on the other hand, extend to the basal ganglia, and in some cases it is a matter of difficulty to judge whether one is justified in dealing with them as subcortical tumours. On the other hand, there are one or two tumours classified as occupying the precentral and postcentral regions which in all probability had originated deep in the white matter, and involved the cortex secondarily, but to such a great extent that they had to be classified as cortical tumours. This topographical diffuseness of tumours involves a certain amount of looseness in classification, but I do not think it invalidates in any essential manner the arguments I have based on this series of cases.

It must be pointed out that certain factors, independent of the optic neuritis itself, have an important influence on clinical observations, such as are recorded in this paper. The most important of these factors is

the duration of the patient's life after the appearance of the disc-changes. With certain tumours, *e.g.*, in the frontal lobe, the patient may live for months or years; while tumours of other regions, such as the fourth ventricle, very quickly terminate in death. Further, craniectomy has a very important influence on optic neuritis, and this operation is performed with varying frequency and at different periods according to the site of the tumour, *e.g.*, cerebellar tumours nearly always undergo operation, rolandic tumours are usually operated on early, while pontine tumours very seldom come into the surgeon's hands. These different conditions have been taken into consideration, as far as possible, in the conclusions stated in the paper.

The complaint may be made that in the following paper I pay little or no attention to the work of other writers on this subject. My reason for not doing so may be very briefly stated. This paper is entirely clinical, and the statements made in it are based on observations on a particular series of cases. The number of cases is not as large as might be desired, but they have been very carefully observed, and what I have sought to do is to form for myself from these cases as clear a clinical picture as I can of optic neuritis as it occurs in cerebral tumours. It is that picture which I desire to place before my readers, and, though critics may find fault with the perspective or the proportions, I would ask them to realize that in depicting it I have striven to keep myself as free as possible from the bias of preconceived notions or authoritative teaching.

Chapter II.

The Incidence of Optic Neuritis in Tumours affecting Different Regions of the Brain.

The 200 cases on which the paper is based fall into the following groups:—

Precentral	30	Extra-cerebellar	19
Postcentral	25	Pontine	15
Temporo-sphenoidal	13	Third Ventricle	4
Deep or Subcortical	32	Fourth Ventricle	5
Optic Thalamus and Mid-brain ...	15	Pituitary	2
Cerebellar	33	Multiple	7

Forty of these 200 cases (exactly 20 per cent.) showed no optic neuritis at any period in their history up to the time of death or operative cure. Of these forty cases, however, there were four in which

a primary or pressure atrophy of both nerves occurred. The development of this condition was in each case due to the direct pressure of the tumour on the chiasma. In two the pituitary body was the site of the tumour; in the third the tumour grew from the floor of the third ventricle, and in the fourth case (No. 25) the tumour originated from the under-surface of the frontal lobes. In each of these cases the atrophy developed without any preceding or accompanying œdema of the nerve head, and in all the loss of vision was very marked and preceded the paling of the discs. This was specially notable in the case (No. 25) of frontal tumour.

In this connection another case of frontal tumour may be cited (No. 1) in which the right lobe was invaded by a tumour which extended up from the orbital surface and also downwards and backwards, involving the tip of the right temporo-sphenoidal lobe, compressing the right optic nerve, the right side of the chiasma and the right optic tract. There was definite left hemianopia, but moderately good central vision in the left eye, though central vision was absent in the right eye. The right optic disc was normal in appearance, though there was a tinge of red in the upper part of the disc which might be taken to indicate commencing capillary congestion. The left optic disc showed intense optic neuritis with much greyish opacity stretching all round and over the neighbouring retina for some distance, one or two hæmorrhages on each side, and a swelling of two dioptres. In this case, then, the pressure of the tumour gave rise to blindness in the right eye, though no primary atrophy had, at the time of death, shown itself in the right disc. In another case which I have recently seen (not included in the present series) the conditions were somewhat similar; here, however, there was a marked primary atrophy in the left eye with an intense neuritis in the right. *Post-mortem* examination in this case revealed a large frontal tumour excavating the under surface of both frontal lobes, but more on the left side than on the right. The left nerve was directly pressed on by the tumour.

These cases show that direct pressure on the intracranial portion of the nerves or on the chiasma may cause loss of vision and pressure atrophy without causing optic neuritis. I shall have occasion to return to this subject later in the paper.

Table I. shows the regions of the brain most frequently affected by tumours without developing neuritis. Twenty of these cases come under the heading of subcortical and pontine tumours, while we see that all the cases of temporo-sphenoidal, cerebellar, and fourth ventricle

TABLE I.

Relative frequency of Cases without Neuritis.

	Cases	No Neuritis	Percentages with no Neuritis
1. Subcortical	32	14	43·75
2. Pontine	15	6	40
3. Extra-cerebellar	19	5	26·315
4. Optic Thalamus and Mid-brain	15	3	20
5. Precentral	30	5[1]	16·6
(*Excluding Case of Primary Atrophy*)	(29)	(4)	(13·793)
6. Multiple	7	1	—
7. Postcentral	25	3	12
8. Third Ventricle and Pituitary	6	3[2]	—
9. Temporo-sphenoidal	13	—	—
10. Cerebellar	33	—	—
11. Fourth Ventricle	5	—	—
Totals	200	40	—

[1] Including one case of primary atrophy. [2] All cases of primary atrophy.

tumours develop neuritis. We must examine in some detail all the cases of subcortical and pontine tumour to see if we can find any means of differentiating between the cases which develop neuritis and those which do not. We must further examine in detail why, in certain cases, neuritis does not arise in connection with tumours of other regions which, as a rule, are associated with it.

Tumours of the pons afford us the simplest problem to start with. Here we find that the development of neuritis is due invariably to the tumour spreading beyond the limits of the pons to invade neighbouring structures. Taking these cases in detail, it is definitely stated in the *post-mortem* reports that the cerebellum was involved in seven of the cases, in five it was not involved, while this point is left doubtful in three cases. Of the seven cases where the cerebellum had been invaded by the tumour, five had, and two had not, neuritis. In these two the invasion of the cerebellum was only of the slightest degree, being restricted to the white matter of the middle peduncle (Cases 173 and 174), so that though, strictly speaking, they must be included amongst the cases in which the cerebellum is involved, practically they should be included with cases of non-invasion of the cerebellum. Of the five cases where it is definitely stated that the cerebellum was not involved, four had no neuritis and in the other (Case 268) there was slight blurring of the right disc before operation with no changes at all in the left eye,

though subsequent to operation quite definite slight neuritis appeared in both eyes. *Post mortem*, this case revealed huge masses of lobulated tumour almost entirely concealing the pons and invading the mesencephalon right forward. In the three cases in which the notes do not make any statement as to the invasion of cerebellum neuritis was definite. There can be little doubt that in all three cases the cerebellum was affected, since it is stated in one (Case 175) that the tumour extended on the left side from the exit of the fifth nerve to the middle of the inferior olives, and at the junction of the pons and medulla involved nearly the whole transverse section of the bulb. In the other two the symptoms certainly indicated cerebellar invasion to such an extent that both were operated on for cerebellar tumour. The examination of these cases may lead us justly to the conclusion that tumours of the pons Varolii do not produce optic neuritis, except by secondary invasion of the adjoining regions, more especially the cerebellum; and this, I think, fully accounts for the well-known fact that pontine tumours only give rise to optic neuritis very late in their history. In other words, when the tumour has invaded these neighbouring structures.

Five cases of extra-cerebellar tumours were also without neuritis. Two of these tumours growing on the trunk of the eighth nerve may come under the category of pontine tumours, in so far as the part of the brain chiefly affected by the growth of these tumours was the pons. Of the remaining three, two were extra-dural tumours and did not involve the cortex of the cerebellum at all. The fifth case was a large tumour in the left posterior fossa pressing on the pons and medulla and cerebellum. The left disc in this case showed some pallor, though no evidence of neuritis.

Excluding multiple tumours, there are 100 cases of tumours involving the cerebral hemispheres. Of these, sixty-eight were cortical and thirty-two deep or subcortical tumours. Of the sixty-eight tumours affecting the cerebral cortex, all those in the tempero-sphenoidal lobe had optic neuritis. With one case of a frontal tumour in which pressure atrophy developed I have already dealt. There remain seven cases in which no neuritis manifested itself, and those seven are divided between the precentral and postcentral regions. In Case 13 the tumour, though at the time of death it involved the whole of the left frontal lobe except the orbital plate, and even pressed across into the left frontal lobe, had obviously originated deep in the hemisphere and had grown down into the basal nuclei as well as up into the frontal cortex. This patient

presented none of the classical symptoms of tumour, having neither headache, vomiting, nor neuritis. The other three cases of precentral tumour without neuritis were of meningeal origin, and in two certainly, and in the third probably, the brain substance was not invaded. There are no characteristics which enable us to differentiate the three cases of postcentral tumour without neuritis from those with neuritis. But, as will be seen later on, the neuritis associated with tumours in this region is often very late in developing, very slight in severity, and short in duration. Further, valuable localizing signs are obtainable frequently early in the history of such cases, so that operative measures may be taken without awaiting the development of changes in the optic disc.

Subcortical tumours show the largest percentage of cases without neuritis, fourteen out of thirty-two. Of the remaining eighteen, five showed only very slight neuritis:—*Case* 69.—The neuritis lasted only a few weeks and subsided without leaving any traces. *Case* 81: Slight blurring of right disc with a little hyperæmia. *Case* 82: No neuritis was present two days before death, disc-changes were found *post mortem*. *Case* 87: Never amounted to a measurable swelling. And *Case* 91: Swelling not more than one dioptre at any time in either eye. In any one of these five cases the existence of neuritis might quite easily have passed unobserved. And, indeed, in three of them it is doubtful whether one is justified in applying the term at all. If we add these cases to the fourteen in which no neuritis occurred, we find that in nineteen cases out of thirty-two (60 per cent.) optic neuritis was a non-existent or insignificant symptom in the clinical history. Here it is rather the cases which get neuritis than those which escape that demand critical examination. Firstly, all the tumours which were confined to the white matter of the hemispheres escaped neuritis, though involvement of the cortex did not necessarily lead to development of neuritis. On the other hand, when growth inwards took place with involvement of the basal nuclei and of the lateral ventricles, optic neuritis almost invariably resulted, though in Case 94 all the basal ganglia were involved in the tumour without neuritis developing.

The single case of multiple tumours, Case 199, which did not develop neuritis adds strength to my argument, for the tumours were two in number—one right subcortical and the other right pontine.

There remain to be considered three cases of tumours affecting the mid-brain and optic thalamus, where optic neuritis was absent. In Cases 103 and 114 we can, I think, find an adequate explanation. In both cases there was great distension of the ventricles. The floor of the

third ventricle was involved in this distention, and there was great and continuous pressure directly on the chiasma. In other words, there was here a condition of direct pressure exactly similar to that dealt with in the first part of this chapter, resulting in the same way in blindness, but without the development of any preceding œdema in the nerve-head. The third case (115) was very similar to Case 94, already mentioned, since here again the basal nuclei on the left side were all attacked by a melanotic sarcoma without neuritis appearing.

We can sum up the preceding section on the incidence of the neuritis in three statements:—

(1) When a tumour directly or indirectly exercises constant pressure on the chiasma or on the optic nerves it is likely to cause a primary pressure atrophy without any preceding œdema of the disc.

(2) Some cases of meningeal tumours where the brain substance is not invaded do not develop optic neuritis.

(3) There are two regions of the brain—the pons Varolii and the white matter of the cerebral hemispheres—in which tumours frequently develop without causing optic neuritis.

Chapter III.

The Severity of the Neuritis.

There are several factors which we have to consider in determining the degree of severity of optic neuritis.[1] Unfortunately, only one of those, the amount of swelling, can be expressed as a direct measurement, but under favourable conditions this particular point can be ascertained with very great accuracy. And in my experience, with rare exceptions, the height of the swelling fairly expresses the severity of the process which we call optic neuritis

The second important feature in estimating the severity of the neuritis is the degree of venous turgescence and capillary congestion present. This forms one of the most striking elements in making up the general ophthalmoscopic picture. Dependent on this is the hæmorrhagic character of the neuritis. Along with the hæmorrhages and also dependent on the degree of venous congestion present there sometimes appear dusky, yellowish patches of exudate. An equally important component of the picture is the extent to which the neighbouring retina is affected by the spreading of the œdema from the neighbourhood of the disc. In a definite proportion of the more severe cases the presence of the spreading œdema is manifested by the formation of what is known

[1] I have purposely made this ophthalmoscopic description very brief. For a full and excellent description *see* Gunn [1].

as a macular fan. This feature is a very definite evidence of neuritis of a gross character, and never appears with the lower degrees of swelling, whereas hæmorrhages occasionally show themselves in cases of neuritis which cannot in any way be described as severe and in association with swelling of quite a small amount. The average swelling calculated from all the cases with hæmorrhages varies but little from the general average of swelling met with in all cases, whereas the general average in cases with macular figures is 0·6 dioptre higher.

I do not consider that the visual loss is to be regarded as a factor in determining the severity of the neuritic process. It is well known that many cases pass through a most severe attack of neuritis, even to the development of macular figures, without the vision being affected in any sensible degree. In a later part of the paper I consider more fully the nature of the relationship between the visual loss and the optic neuritis.

TABLE II.

Severity of Neuritis.

	Average swelling	Highest swelling observed	Cases with consecutive atrophy when first seen	Cases with hæmorrhages	Percentages with hæmorrhages	Average swelling in cases with hæmorrhages	Cases with macular figures
Precentral	4·8 D	6·5 D	2	15 out of 23	65	4·7 D	4
Postcentral	3·6 D	6·0 D	—	9 out of 22	41	4·2 D	4
Temporo-sphenoidal ...	4·6 D	6·0 D	—	8 out of 13	61	4·6 D	2
Subcortical	3·5 D	7·0 D	2	7 out of 16	44	3·8 D	—
Optic Thal. and Mid-brain ..	5·0 D	8·0 D	1	7 out of 11	64	5·3 D	2
Multiple	5·3 D	7·0 D	1	2 out of 5	—	—	—
Cerebellar	4·6 D	7·0 D	8	10 out of 25	40	4·8 D	7
Extra-cerebellar	5·0 D	6·0 D	—	9 out of 14	64	4·9 D	2
Pons	5·3 D	7·0 D	—	4 out of 9	44	5·3 D	1
Third Ventricle	—	5·5 D	—	3 out of 8	37	4·5 D	—
Fourth Ventricle	4·4 D	5·0 D	—				
Totals	4·5 D[1]	—	—	74 out of 146[2]	—	—	22 out of 146[3]

[1] Mean swelling in 212 discs at highest observed swelling.
[2] Cases with consecutive atrophy excluded.
[3] Mean swelling of discs in 22 cases equalled 5·1 D.

There are certain points which come out in a striking fashion in an examination of this table. In the first place it is quite obvious that the neuritis is much less severe in subcortical and postcentral tumours

than with those anywhere else. Not only is this so, but also in a considerable number of cases in both those groups the process was also of very short duration. A proof of its comparatively late development in the history of such tumours is afforded by the fact that out of thirty cases in which neuritis developed after admission of the patient into the hospital, ten were cases of postcentral tumour and seven were subcortical (see Table III.). On the other hand, pontine tumours, when they do develop optic neuritis, manifest it in a very severe form, and the same may be said of extra-cerebellar tumours.

Judged by the swelling alone, the severity of the neuritis in cases of cerebellar tumour would seem to be little above the average. And in this class the proportion of cases that showed hæmorrhages was not very high, yet we find a larger proportion of cases with macular figures than in any other class. The explanation of the position which this region occupies in the scale of severity seems to lie in the rapidity with which atrophy supervenes in many cases of cerebellar tumour; eight of the fourteen cases in which there was so-called consecutive atrophy at the time the patients were admitted to the hospital were cerebellar tumours. It is probable that these cases had passed through a neuritis of considerable severity during the earlier stages of tumour development, the details of which, if they had been available, would have sensibly altered the relative position of cerebellar tumours.

We arrive, then, at the following tentative conclusions based on the available material as to the incidence and severity of optic neuritis in tumours of the different brain regions:—

(1) Precentral tumours are nearly always associated with neuritis fairly severe in character.

(2) Postcentral tumours are nearly always associated with neuritis, as a rule moderate, and often of very short duration.

(3) Temporo-sphenoidal tumours are always associated with neuritis of about the same degree of severity as in frontal tumours.

(4) Of subcortical tumours about one half develop neuritis—as a rule, moderate in degree—and, as in the case of parietal tumours, frequently of short duration.

(5) Optic thalamus and mid-brain tumours are almost invariably associated with optic neuritis of very great severity.

(6) Cerebellar tumours are constantly accompanied by neuritis of a grave character.

(7) Extra-cerebellar tumours, as a rule, develop neuritis of a grave character.

(8) Of pontine tumours, about one half only develop optic neuritis, and then only when neighbouring parts of the brain, especially the cerebellum, have become involved. The neuritis when it does develop is usually very severe.

(9) Ventricular tumours develop a moderate neuritis.[1]

Chapter IV.

The Relationship of the Amount of Neuritis to the Side of the Tumour.

The important discussion which followed the reading of a paper by the author before the Ophthalmological Society of the United Kingdom in the early part of 1908 mainly bore on the question of the value of a difference in the amount of optic neuritis in the two eyes as indicating the side of the tumour. The writer was fully conscious that the views which he then expressed were not in accordance with the teaching of many authorities. Any statement which seeks to controvert the opinion held by men of such great experience in neurology as Sir Victor Horsley [2] and Sir William Gowers must needs have strong evidence behind it if it is to secure acceptance. The practical importance of the question can hardly be over estimated, and it is essential that the cases on which any conclusions may be based should be submitted to a rigid scrutiny.

It may be stated as a general rule that when neuritis starts in one eye earlier than in the other, only occasionally does the neuritis remain greater in the eye which first shows it; in most cases at the height of the swelling the neuritis becomes equal in both eyes. It does happen rarely that one eye may show greater neuritis in the earlier stages, and with an increasing neuritis in both eyes the opposite eye may show the greater neuritis in later stages.

In thirty cases of the present series the neuritis developed while the patients were under observation. In thirteen of those it appeared simultaneously in the two eyes. In eleven it developed first in the opposite eye, and in six only did it develop first in the eye on the same side as the tumours (*see* Table III.).

In dealing with the question of the amount of neuritis, we can only take those cases in which no signs of subsidence or atrophy had made their appearance. This will lead to the exclusion of fifty-eight out of

[1] In tumours of the floor of the third ventricle a simple pressure atrophy may replace the neuritis.

the 160 cases in which neuritis developed, leaving 102 cases. I have put down as equal in swelling all cases in which the difference between the measurement in the two eyes does not exceed 0·5 dioptre. As will be seen from the table, the numbers come out that in fifty-four cases the swelling was equal in two eyes. In twenty-five the swelling was greatest in the eye on the side of the tumour, and in twenty-three it was greatest in the opposite eye.

Intrinsic cerebellar tumours formed the class in which the eye of the same side most frequently showed the greatest neuritis. If, however, we sum up the subtentorial tumours, we find that in nine the greatest swelling was in the eye of same side, and in six it was in the opposite eye; while in the case of supratentorial tumours the numbers are sixteen for the eye of same side and sixteen for the opposite eye.

In the single case of multiple tumours, one was subtentorial and one supratentorial, but both were on the left side.

TABLE III.

Site.	Neuritis, commencing in eye of same side	Neuritis, commencing in eye of opposite side	Neuritis, commencing simultaneously in both eyes	Total	Greatest swelling in eye of same side	Greatest swelling in eye of opposite side	Swelling equal in both eyes	Total
Precentral	1	2	2	5	4	4	11	19
Postcentral	3	3	4	10	6	3	8	17
Temporo-sphenoidal	1	—	—	1	1	1	7	9
Subcortical	—	3	4	7	2	4	7	13
Optic Thal. and Mid-brain	—	—	1	1	3	3	3	9
Multiple	—	1	—	1	—	1	3	4
Cerebellar	1	—	—	1	7	1	9	17
Extra-cerebellar	—	1	1	2	2	3	4	9
Pontine	—	1	1	2	—	2	2	4
Third and Lateral Ventricle	—	—	—	—	—	1	—	1
Totals	6	11	13	30	25	23	54	102

It is impossible to go into the details of the whole of this series of forty-eight cases, in which there was definite inequality in the amount of neuritis. But we may subdivide them into four classes according to the amount of inequality, and then deal in tabular form with the more important of these classes. The first subdivision includes three cases in which the neuritis had affected only one eye at the time of death or operation.

TABLE IV.

Neuritis affecting only one eye at the time of death or operation.

Case	Site of Tumour	Amount of Neuritis		Remarks
		Right Eye	Left Eye	
1	Right precentral	None	+ 2·0 D	Neuritis intense in character with hæmorrhages in left eye
34	Right rolandic	Haziness, no swelling	+ 1·5 D	Edges of left disc blurred
200	Left ascending frontal and left extra-cerebellar	Commencing neuritis	Normal	Neuritis early but definite in right eye

It will be seen that in each of these three cases the neuritis at the time of death or of operative interference had appeared definitely in one eye only, and in each case it was the eye on the side opposite to the tumour which showed the neuritis. To the first case I have already referred in the early part of Chapter II., where I have given what I think is the true explanation of the non-development of the neuritis in the right eye. In the other two cases the neuritis, though of short duration, was perfectly definite in character.

The second subdivision consists of cases which showed a difference of two dioptres or more between the highest measured swelling in the two eyes.

TABLE V.

Cases showing 2 D *or more difference between the swelling in the two eyes.*

Case	Site of Tumour	Amount of Neuritis		Remarks
		Right Eye	Left Eye	
3	Right Precentral ...	1 D	4 D	Vision very bad before neuritis
22	Right Precentral ...	4 D	6·5 D	Neuritis equal in earlier stages
47	Left Postcentral ...	3 D	commencing	Slight blurring in left eye three days before death
73	Left Subcortical ...	3 D	1 D	Neuritis developed first in right eye
113	Mid-brain, mostly left side	8-10 D	7 D	Very intense neuritis. Tumour much greater on left side than on right
154	Left Cerebellar ...	6 D	3 D	
185	Left lateral Ventricle and third Ventricle	5·5 D	3·5 D	
40	Right Postcentral ...	2 D	commencing	Swelling measurable in right eye only on day of death
42	Right Hemisphere ...	3·5 D	1·5 D	Large extra-cerebral blood-cyst
101	Right Optic Thalamus	6 D	4 D	
153	Left Extra-cerebellar	3 D	5 D	

The first seven cases in this table show a very much greater amount of swelling in the eye away from the side of the tumour than in the eye on the same side. In the last four cases it will be seen that it was the eye on the side of the tumour which had the greater swelling. In all these cases, apart altogether from the question of measurement, there were definite differences in the ophthalmoscopic pictures presented by the two eyes.

The third subdivision includes five cases in which the difference in the swelling between the two eyes was 1·5 dioptre. In four of these it was the eye on the side of the tumour which had the greatest swelling, and in one it was the opposite eye. Taking these first three subdivisions together, there are eight cases in which the eye on the side of the tumour showed the greatest swelling and eleven cases in which the opposite eye showed the most.

In the remaining cases the difference amounted to one dioptre only, and in this subdivision there were seventeen cases where the eye on the side of the tumour showed most swelling as against twelve where the opposite eye was most affected, making up the totals, as seen on Table III., to twenty-five and twenty-three respectively.

In a small number of cases the neuritis took on a hæmorrhagic character in one eye only, and while I do not lay any great stress on hæmorrhages as an indication of severity of neuritis, yet I give the numbers as showing that even in this characteristic it was occasionally the opposite eye which showed hæmorrhages. In twelve cases these appeared in the eye of the side of the tumour, and in five cases in the opposite eye.

As I have already said, there is reason to doubt the close relationship between the visual result and the neuritis, but we do find a few cases in which the vision was much more affected in one eye than in the other as the neuritis subsided. There were nine such cases, and in four it was the eye on the side of the tumour in which the vision was most affected, and in five it was the opposite eye.

In concluding this section, I may for a moment intrude a personal statement. Before I started to analyse these statistics, I should have been prepared to state, as my general impression, that the neuritis was greater on the side of the tumour. The few exceptions that I had seen—*e.g.*, Case 1—were, as I thought, capable of simple explanation. But, as the exceptions increased in number, I was forced to realize that the point was not one that could be regarded as of value in localization. Even if the number of cases where the opposite eye is the more affected

were much smaller than it is, so long as we are unable to explain why in some cases it should be more affected we cannot assume that a difference in the amount of neuritis is a sign of localizing value.

Chapter V.

Nature of Tumour in Relationship to Neuritis.

The nature of the tumour was ascertained in 150 cases. Of these, twenty-nine had no neuritis (19·3 per cent.), so that, on the whole, they may be taken as making a fairly representative collection. An examination of the cases in detail does not lend much support to the idea that the nature of the tumour plays any important part in determining the occurrence of optic neuritis except in so far as the nature of the tumour may determine the locality. Gliomata formed a very considerable proportion of the whole, there being sixty-three cases. Of these, thirteen had no neuritis, so that in this case at any rate the percentage, 20 to 63, without neuritis is the same as we find in tumour cases in general.

Table VI.

Nature of Tumour	Glioma		Sarcoma		Cysts		Endothelioma		Tubercle		Fibroma		Carcinoma		Gumma		Papilloma		Total	
	Neuritis present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Frontal ...	13	1	—	2	1	1	5	1	—	—	1	—	1	—	1	—	—	—	22	5
Parietal ...	4	—	2	—	4	—	1	—	—	—	—	—	—	1	1	—	—	—	12	1
Temp.-sphen. ...	3	—	4	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	9	—
Subcortical ...	3	7	2	—	3	—	1	—	—	—	—	—	—	—	—	—	—	—	9	7
Optic Thal. and Mid-brain ...	6	—	1	2	—	—	—	—	2	1	—	—	—	—	—	—	—	—	9	3
Multiple ...	—	—	—	—	—	—	2	—	—	—	—	—	4	—	—	1	—	—	6	1
Cerebellar ...	11	—	5	—	6	—	—	—	4	—	—	—	—	—	1	—	—	—	27	—
Extra-cerebellar	1	1	1	2	—	—	1	1	—	—	9	—	—	1	—	—	—	—	12	5
Pontine ...	5	4	1	1	—	1	—	—	2	—	—	—	—	—	—	—	—	—	8	6
Ventricular ...	4	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	2	—	7	1
Totals	50	13	16	7	14	3	12	2	9	1	10	—	5	2	3	1	2	—	121	29
Percentage without neuritis...	20·63		26.09		17·64		14·28		10		—		28·57		25		—		19·3	

In some of the other cases the numbers are too small to afford a trustworthy basis for percentage classification, but I give the list in the inverse order of the frequency of neuritis.

The first seven cases in this table show a very much greater amount of swelling in the eye away from the side of the tumour than in the eye on the same side. In the last four cases it will be seen that it was the eye on the side of the tumour which had the greater swelling. In all these cases, apart altogether from the question of measurement, there were definite differences in the ophthalmoscopic pictures presented by the two eyes.

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	Neuritis present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Frontal ...	13	1	—	2	1	1	5	1	—	—	1	—	1	—	1	—	—	—	22	5
Parietal ...	4	—	2	—	4	—	1	—	—	—	—	—	—	1	1	—	—	—	12	1
Temp.-sphen. ...	3	—	4	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	9	—
Subcortical ...	3	7	2	—	3	—	1	—	—	—	—	—	—	—	—	—	—	—	9	7
Optic Thal. and Mid-brain ...	6	—	1	2	—	—	—	—	2	1	—	—	—	—	—	—	—	—	9	3
Multiple ...	—	—	—	—	—	—	2	—	—	—	—	—	4	—	—	1	—	—	6	1
Cerebellar ...	11	—	5	—	6	—	—	—	4	—	—	—	—	—	1	—	—	—	27	—
Extra-cerebellar	1	1	1	2	—	—	1	1	—	—	9	—	—	1	—	—	—	—	12	5
Pontine ...	5	4	1	1	—	1	—	—	2	—	—	—	—	—	—	—	—	—	8	6
Ventricular ...	4	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	2	—	7	1
Totals	50	13	16	7	14	3	12	2	9	1	10	—	5	2	3	1	2	—	121	29
Percentage without neuritis...	20·63		26.09		17·64		14·28		10		—		28·57		25		—		19·3	

In some of the other cases the numbers are too small to afford a trustworthy basis for percentage classification, but I give the list in the inverse order of the frequency of neuritis.

No Neuritis.

Carcinoma	2 out of 7 cases	...	—
Sarcoma	7 out of 23 cases	...	26·1 per cent.
Gumma	1 out of 4 cases	...	—
Glioma	13 out of 63 cases	...	20·6 per cent.
Cysts	3 out of 17 cases	...	17·6 per cent.
Endothelioma	2 out of 14 cases	...	14·3 per cent.
Tubercle	1 out of 10 cases	...	—
Fibroma	0 out of 10 cases	...	—
Papilloma	0 out of 2 cases	...	—
	29 out of 150 cases	...	19·3 per cent.

At first sight it certainly seems a little curious that this list should be headed by the two classes of tumours which show the most malignancy. But one of the two cases of carcinoma was an extra-dural tumour in the cerebellar region which did not invade the brain substance at all, and the other was quite a small tumour in the parietal region.

The elucidation of the cases of sarcomata presents greater difficulties. We find that one of the seven cases is the mid-brain tumour (Case 103) for which we have already attempted to provide an explanation of the non-occurrence of optic neuritis in the dilatation of the third ventricle; if we except this case the percentage is brought practically down to the normal. The intracranial tension in at least four of the remaining cases was high, and in one of them very high (Case 158). These sarcomatous tumours were not limited to any one region. When we come to the other end of the list we find that practically all the cases of tubercle were associated with optic neuritis. The explanation of this seems to be that the tuberculous growths were much more frequent in the mid-brain and cerebellum than in any other part of the brain. A similar argument applies in the case of a fibromata, where nine of the ten cases described were extra-cerebellar tumours. The two cases of papilloma described were both intra-ventricular tumours and both associated with neuritis.

A critical examination of the relation existing between the nature of the tumour and the optic neuritis forces us to conclude that there is nothing in the nature of the tumour itself which determines the onset of neuritis. Not even does rapidity of growth seem to play any great part, nor size, as gross neuritis may be caused by a very small tumour in one place, while a very large tumour may be present in another place without any change appearing in either disc. In so far as the nature of the

tumour determines its location, just so far and no further does it seem to determine its relationship to the neuritis.

If we examine the effect of this conclusion on the question as to the pathogenesis of the optic disc phenomena, we see that, in so far as it goes, it is against the toxin hypotheses, since the rate of breaking down of brain matter and the rapidity of development of toxins will not in any way depend on the position of the tumour, but will depend on its nature and on the rapidity of its growth. For example, gliomata tend to break down readily, and yet, as we have seen, they do not proportionately cause a greater amount of optic neuritis, while fibromata show little tendency to break down themselves or to cause breaking down of brain substance, and yet most of them are associated with neuritis.

Chapter VI.

The Relationship of Optic Neuritis to Intracranial Tension and to the occurrence of Meningitis.

Evidence of the state of intracranial tension during life is only obtainable directly in cases which are submitted to operation. There is little doubt that the tension varies considerably from time to time, and that the attacks of increased headache, giddiness, vomiting and temporary dimness of sight coincide with periods of raised tension. The reports of the amount of intracranial tension at the time of operation depend on the personal equation of the observer, and any distinction between cases must be, to a considerable extent, an arbitrary one.

Post-mortem evidences must depend to almost as great an extent on the duration of the raised tension as on the amount of it. *Post-mortem* evidences will also vary with the position of the tumour. Thus a supratentorial tumour will be more likely to show much flattening of the cerebral convolutions when the tension has been raised for some time, while a subtentorial tumour will be more likely to show a large pressure cone at the foramen magnum.

In a considerable number of cases there is unfortunately no indication in the notes as to the condition of the intracranial tension. I have attempted to subdivide the other cases into three classes.

Class I. showed evidences of very high intracranial tension—*e.g.*, great bulging of the dura at the time of operation or a very marked pressure cone or much flattening of the convolutions or much distended ventricles at the autopsy.

Class II., cases which gave definite evidence of raised tension at operation or *post mortem*, though not of such a gross character as in Class I.

Class III., where the operation notes definitely state that the tension was not raised or where the *post mortem* revealed no flattening of the convolutions nor distension of the ventricles.

TABLE VII.

Intra-cranial Tension Cases with Neuritis	Very high	High	Slight or normal	
Precentral	3	6	1	10
Postcentral	2	6	1	9
Temporo-sphenoidal	3	7	1	11
Subcortical	1	12	—	13
Multiple	—	—	1	1
Optic Thalamus and Mid-brain	5	6	1	12
Cerebellar	11	14	3	28
Extra-cerebellar	4	5	1	10
Pontine	5	1	—	6
Third Ventricle	2	1	—	3
Fourth Ventricle	2	3	—	5
	38	61	9	108

TABLE VIII.

Intra-cranial Tension Cases without Neuritis	Very high	High	Slight or normal	
Precentral	—	3	—	3
Postcentral	—	1	—	1
Temporo-sphenoidal	—	—	—	—
Subcortical	1	2	2	5
Multiple	—	1	—	1
Optic Thalamus and Mid-brain	2	1	—	3
Cerebellar	—	—	—	—
Extra-cerebellar	1	1	—	2
Pontine	—	1	5	6
Third Ventricle	—	—	1	1
Fourth Ventricle	—	—	—	—
Totals	4	10	8	22
Percentage of Total Cases in each class ...	9·523 %	14·084 %	47·05 %	

Taking the tables as a whole, they seem to favour the hypothesis that the occurrence of neuritis is closely related to the amount of intra-

cranial tension, but I do not think we have at the present time evidence enough to justify us in saying that the relationship is one of cause and effect. It is possible that the raised intracranial tension and the optic neuritis are two concurrent results of one common cause. For instance, a change in intracranial conditions due to the presence of the tumour may cause an œdema of brain tissue which, in course of time, spreads to the optic nerve, and at the same time may play a part in raising the intracranial tension.

Table VIII. shows four cases in which there was very high tension without optic neuritis. I have already dealt in detail with the two mid-brain cases (103 and 114) in Chapter II., and have offered an hypothesis to explain the non-appearance of neuritis, despite the very high tension. The other two cases (86 and 158) remain unexplained exceptions to the rule, that very high intra-cranial tension is accompanied by optic neuritis.

Pontine tumours are of special interest in this connection. I have laid great stress on the conditions under which these tumours produce neuritis, and a comparison of Tables VII. and VIII. shows that the appearance of neuritis and a great rise in intracranial tension are always associated. In each table there are six cases. Five of those with neuritis had very high tension, five without neuritis had normal intra-cranial tension. It is much to be regretted that we cannot in a similar manner contrast the cases of subcortical tumour with and without neuritis, but, unfortunately, in nine out of the fourteen cases without neuritis the notes do not afford any evidence as to the condition of the intracranial tension. One would like to suppose that this was because the tension was not raised. To make such a supposition in this case would involve doing the same in the larger number of cases of cortical tumour (precentral and postcentral) with neuritis in which notes of intracranial tension are equally lacking.

The possibility of optic neuritis being due to an inflammation spreading from the meninges down the nerve-sheaths may be dealt with very briefly. It must be understood that the description of the meninges in the reports is in the large majority of cases based only on the macroscopic appearances. In twenty-eight cases only was there any meningeal change noted. In twelve of these this consisted of nothing more than inflammatory adhesions confined to the surface affected by the tumour. In seven cases there was post-operative meningitis which could have had nothing to do with the development of the neuritis, and, indeed, in four cases in which the meningeal inflammation was most generalized

there was no neuritis. In the great majority of *post-mortem* reports the meninges were stated to be healthy.

Chapter VII.

The Vision in Cases of Cerebral Tumour.

I have stated in an earlier part of this paper that there is grave reason to doubt that the loss of vision that occurs in cases of cerebral tumour is due to the condition which we call optic neuritis. Further, we may ask the question whether the atrophy which appears later in the history of the case is really consecutive on this process or is a simple pressure atrophy. Before I proceed to the consideration of this, there are one or two points about the vision with which I wish to deal. In some cases, of course, the mental condition of patients precluded the possibility of accurate subjective testing at any time during the history of the case. In other cases the vision could be tested before operation, but the effect of the operation itself on either the vision or the neuritis could not be noted.

There were 101 cases with neuritis in which a fairly full history of the state of the vision could be obtained, and of the cases without neuritis the vision could be tested in a large proportion.

Table IX.

Visual Results—Operation Cases	$\frac{6}{9}-\frac{6}{12}$	$\frac{6}{18}-\frac{6}{24}$	$\frac{6}{60}$—finger counting	P.L.—blind	One eye bad vision: Same side	One eye bad vision: Opp. side	Vision defective for reasons apart from Neuritis
Precental	7	1	—	1	1	1	1
Postcentral	6	4	2	2	1	—	2
Temporo-sphenoidal	—	1	—	—	1	—	—
Subcortical	4	—	—	—	—	—	—
Optic Thalamus and Mid-brain	—	—	—	3	—	—	—
Cerebellar	7	1	—	4	1	2	—
Extra-cerebellar	3	—	1	—	—	—	—
Pontine	—	—	—	—	—	—	—
Ventricular	—	—	—	—	—	—	—
Totals	27	7	3	10	4	3	3
	[1]57·44%	14·9%	8%	21·27%			
	[2]34 = 72·34%		13 = 27·66%				

47 Cases.

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[1] Fair vision, 22 out of 30 = 73·3%
[2] Good vision, 18 out of 30 = 60%

TABLE X.

Visual Results—Non-Operative Cases	$\frac{6}{6}$—$\frac{6}{18}$	$\frac{6}{24}$—$\frac{6}{60}$	$\frac{6}{\infty}$—finger counting	P.L.—blind	One eye bad vision		Vision defective for reasons apart from Neuritis
					Same side	Opp. side	
Precentral	—	1	1	1	—	—	1
Postcentral	2	1	—	—	—	—	—
Temporo-sphenoidal	2	2	—	1	—	—	—
Subcortical	4	1	1	1	—	1	—
Optic Thalamus and Mid-brain	—	1	1	2	—	1	—
Cerebellar	1	—	2	4	—	—	—
Extra-cerebellar	—	1	1	1	—	—	—
Pontine	1	1	—	3	—	—	—
Ventricular	2	—	1	1	—	—	—
Totals	12	8	7	14	—	2	1
	29·27 %	19·51 %	17·07 %	34·14 %			
	20 = 48·78 %		21 = 51·22 %				
	41 Cases.						

The first point I wish to deal with is the beneficial effect of operation on vision. For this purpose we must exclude the cases in which atrophy was obvious before the patient came under observation. There remain eighty-eight cases, forty-seven of which were operated on and forty-one were not.

These tables show how very beneficial operation is in saving sight. Table IX. gives a larger number of cases than I gave in my paper in Volume XXV. of the *Transactions of the Ophthalmological Society*, but the percentages remain unchanged. The vision in Table X. is the last recorded before death. As I am dealing in the present paper with confirmed cases alone, and as the confirmation of a case not operated on can only take place after death, it is not right to make too many inferences from a comparison of these tables. As regards Table IX., there is one point of very considerable practical importance. Of the forty-seven cases mentioned in it, twenty-eight were alive when last heard of, many of them in perfectly good health. If we distribute these into their respective classes as regards vision, we find that of the twenty-seven with good vision ($\frac{6}{6}$ to $\frac{6}{12}$), nineteen are still alive; of the seven with moderately good vision ($\frac{6}{18}$ to $\frac{6}{36}$), six are still alive; so that of thirty-four cases operated on retaining moderately good vision, twenty-five are alive, while only three of the thirteen with bad vision are alive. This, I think, has an important bearing on the question of the time to choose for operation in such cases, since it would seem to be obvious that if

operation is deferred till visual loss is well marked, the chance of the patient surviving is very much diminished. I return to this point later on.

In Table XI. I give the visual results in cases with optic neuritis as they appeared in tumours of different parts of the brain.

TABLE XI.

Visual Results in cases of Optic Neuritis, excluding cases which died within a few weeks of operation or whose vision could not be taken [but including cases of consecutive atrophy when first seen].

	Vision $\frac{6}{6}$—$\frac{6}{36}$	Vision $\frac{6}{60}$—blind	Percentage of cases vision badly affected
1. Optic Thalamus and Mid-brain	1	7	87·5
2. Cerebellar	9	18	66·6
3. Pontine	2	3	60·0
4. Ventricular	2	2	50·0
5. Extra-cerebellar	4	3	42·85
6. Frontal	9	5	35·71
7. Subcortical	9	4	30·77
8. Parietal	13	4	23·53
9. Temporo-sphenoidal	5	1	16·6
Totals	54	47	46·53

This table shows that the tumours which are most likely to cause ventricular distension are those which cause the greatest loss of vision.

I wish to suggest as a possibility—worthy, at any rate, of being seriously considered—that the affection of vision which takes place in cerebral tumours is not of necessity the result of the affection of the nerve-head which we indiscriminately term papillitis, optic neuritis, or choked disc. There are several reasons which can be adduced in favour of regarding the visual loss and the papillary œdema as more or less independent of one another. (1) There is the undoubted fact that many cases go through a most severe attack of optic neuritis without the visual acuity being affected in the slightest degree. (2) I pointed out in a previous paper that attacks of temporary amaurosis are frequently met with in cases of cerebral tumour, that these attacks are always associated with increased headache and giddiness, that they may be met with in cases in which no disc-changes were manifest, and did occur in three cases in which no neuritis ever did develop. (3) I have already spoken of two cases of tumours in the mid-brain which did not develop any optic

neuritis. One of these cases (H. F.) had become quite blind within about four weeks, though the discs were normal in appearance. Of the other, the mental condition did not allow the vision to be tested, but the pupillary reflex to light was completely lost. (4) In certain cases in which neuritis did develop, the failure of vision distinctly preceded the appearance of any disc-changes. (5) The vision is most affected in cases in which there is the greatest likelihood of distention of the third ventricle [compare visual table (XI.) with tables of intracranial tension (VII. and VIII.)]. (6) The recovery of vision after operation in many cases takes place at a very much more rapid pace than the subsidence of the neuritis. (7) In certain cases of the present series we have evidence that direct pressure of the tumour on the nerve or the chiasma causes blindness, *e.g.*, and this blindness may exist for some time before signs of descending atrophy manifest themselves in the disc. (8) Frequently cases which have been seen to pass through an attack of papillitis which has completely subsided present a condition of disc which it is practically impossible to distinguish from the disc of a primary atrophy.

These points, I think, must suggest that the visual loss and the subsequent atrophy may, at least in some cases, depend on some factor other than the papillary changes, and I would suggest the possibility that that factor is the direct pressure of the distended floor of the third ventricle on the chiasma. And I think this will account for the fact that the vision is less affected in temporo-sphenoidal tumours than in any other class of case, though in all other respects temporo-sphenoidal tumours stand so high up in the degree to which they are affected by optic neuritis; and it will also, I think, account for the bad visual results in all the cases in which there is a likelihood of blockage of the aqueduct of Sylvius.

If we accept this hypothesis provisionally as it affects the sight, it may be that the atrophy which appears in the later stages of this process is also to be regarded as analogous to any other pressure atrophy, only modified by the co-existence of an œdema in its earlier stages, and if this is so we may have to look to the chiasmal end of the optic nerves rather than the disc end for the earliest signs of the atrophic process. The point is one of great practical importance, since in many cases it is necessary to perform a decompression operation to save sight where no definite localization of the tumour can be made; and, if this hypothesis be correct it is the commencement of visual failure that should be taken as an indication for palliative trephining rather than the occurrence of optic

neuritis. All the evidence goes to show that if cases are operated on while vision is little affected, the chances for the patient surviving are good, and this would seem to be true even when the neuritis has been in existence for a prolonged period. On the other hand, the worse the vision the poorer is the patient's chance of surviving. This, however, may simply be due to the fact that it is in mid-brain and subtentorial tumours that the vision is most likely to be seriously affected.

Chapter VIII.

The Age-incidence of Optic Neuritis in Cerebral Tumours.

Before we can properly discuss the question of whether optic neuritis diminishes in frequency and in severity with increasing years, we must first see what the age-incidence of tumours in general is. The cases in the present series varied in age from 1½ years up to 68, but the enormous majority of the cases were between 15 and 50. The average age of all the cases was 34. Table XII. gives the age-incidence of the tumours in general, apart from any question of neuritis.

Table XII.

Age-incidence of Tumours in different regions of the Brain.

Site of Tumour.	Average age.	Cases under 30.	Cases between 30 and 40.	Cases over 40.
Precentral	37	9	12	8
Postcentral	38	5	9	10
Temporo-sphenoidal	34	4	4	4
Subcortical	41	7	9	16
Optic Thalamus and Mid-brain ...	27	9	3	2
Cerebellar	15	27	3	2
Extra-cerebellar	39	5	6	8
Pontine	15	12	—	3
Ventricular	36	4	1	4
Multiple	46	1	2	4
Totals	—	83	49	61

If we take the mean of the ages of patients with neuritis we find that it is 32, two years less than the mean age for all tumours. On the other hand, if we take the mean age of cases without neuritis, it is 40, six years higher than the general average. An examination of Table XIII. will, I think, serve to show that this does not really mean that optic neuritis tends to become less frequent because of advancing age. The true explanation lies in the fact that all cerebellar tumours get optic

TABLE XIII.

Age-incidence in Tumours with and without Neuritis.

Site.	With Neuritis.			Without Neuritis.		
	Cases under 30	Cases between 30 and 40	Cases over 40	Cases under 30	Cases between 30 and 40	Cases over 40
Cortical	17	20	18	—	3	3
Subcortical	4	6	8	3	4	9
Optic Thalamus and Mid-brain ...	7	3	1	2	—	1
Cerebellar	27	3	2	—	—	—
Extra-cerebellar	2	6	6	2	1	2
Pontine	9	—	—	3	—	3
Ventricular	4	1	3	—	—	—
Multiple	1	1	4	—	1	—
Totals	71	40	42	10	9	18

neuritis, and cerebellar tumours are more particularly prone to occur in the early years of life, as shown in Table XII., whereas subcortical tumours, which frequently escape without neuritis, are much more frequent in later life. A comparison of the two parts of Table XIII. reveals how much the different age-incidence in the two classes depends on the one hand on the preponderance of cerebellar tumours, and on the other on the preponderance of subcortical tumours. And I think it must be admitted that, apart from these two regions, age-incidence of cases with neuritis and without neuritis would be very similar. The conclusion which I have come to from a careful examination of this series of cases is that age in itself has little or no influence in determining the onset of neuritis.

The age-incidence of cases which showed hæmorrhages corresponded almost exactly with that of the cases with neuritis, the average age being 33. The average age of the cases with macular figures is definitely lower—27 years. The fact that the cerebellar cases form such a definite proportion with this change would have led us to anticipate some such result.

CHAPTER IX.

Summary of Conclusions.

I may briefly recapitulate the main conclusions which the examination of this series of 200 cases has led me to:—

(1) Tumours directly or indirectly exercising constant pressure on

the chiasma, or on the optic nerves, may cause primary pressure atrophy without any preceding œdema of the disc.

(2) The great majority of tumours affecting the grey matter of the cortex cerebri have optic neuritis, the severity of which seems to vary inversely with the distance of the part affected from the chiasma.

(3) Tumours lying deep in the white matter of the cerebral hemispheres do not, as a rule, develop optic neuritis until they invade either the cortex or the basal ganglia. They are most likely to develop optic neuritis when they spread in the latter direction.

(4) Tumours affecting the optic thalamus, the mid-brain, the cerebellum and the ventricles are almost invariably associated with optic neuritis.

(5) Pontine tumours and some extra-cerebellar tumours which are closely allied to pontine tumours do not develop optic neuritis until neighbouring regions, especially the cerebellum, are invaded.

(6) A difference in the intensity of the neuritis in the two eyes is met with in about 50 per cent. of all cases. The neuritis in some cases is greater in the eye on the side of the tumour, and in some cases is greater in the opposite eye. When a difference exists it should not be regarded as of localizing value.

(7) The nature of a tumour does not in itself play any part in determining the onset of neuritis, except in so far as the nature of the tumour determines its location.

(8) A close relationship seems to exist between the occurrence of neuritis and the amount of intracranial tension, but there is as yet nothing to justify us in saying that the relationship is one of cause and effect.

(9) Meningeal inflammation is rare in cerebral tumours, and when it does occur is, in the majority of cases, localized to the actual tumour area and plays no part in the causation of optic neuritis.

(10) There are reasons for thinking that the diminution of visual acuity and the œdema of the optic nerve-head are more or less independent of one another, and are not related to one another as cause and effect.

(11) The atrophy of the nerve in some cases at least is probably a simple pressure or descending atrophy starting from the chiasmal end of the nerve and exactly analogous to the primary atrophies that occur quite apart from any œdema of the disc.

(12) Age in itself has little or no relationship to the occurrence of neuritis.

The desire for brevity has given a greater appearance of dogmatism to these twelve conclusions than I would wish to convey, but I can only hope that readers will bear in mind that they are based on this particular series of cases alone, and I have little doubt that future work will introduce many modifications and qualifications into these conclusions.

Literature.

[1] Gunn, Marcus. *British Medical Journal*, October 26, 1907.
[2] Horsley, Sir Victor. Presidential Address, *British Medical Association*, 1906, and Oxford Address, July, 1908. *Ophthalmoscope*, September, 1908, p. 658.
[3] Paton, Leslie. *Trans. Ophthalmological Soc.*, 1905, vol. xxv., p. 129.

Publications Recently Received.

[*Notes on a book under this heading do not preclude a subsequent review.*]

Ueber die Kerne des Menschlichen Rückenmarks. Von L. Jacobsohn. S. 72, mit 9 Tafeln. Berlin: Königl. Akadamie der Wissenschaften, 1908.

This monograph gives a detailed description of the arrangement of the nerve cells in the grey matter of the spinal cord, which the author has studied in serial sections. The typical arrangement in each segment is illustrated by drawings and described in the text in much the same manner as the same subject was treated by Bruce in his well-known "Atlas of the Spinal Cord." In Jacobsohn's work, however, more attention is given to the cells of the dorsal horns and to the irregular groups which lie elsewhere in the grey matter. Unhappily these cells have received as yet very little attention in the investigation of spinal cords affected by different pathological conditions, and if this monograph succeeds in exciting interest in them it will undoubtedly repay the enormous amount of labour expended on it.

Einführung in die Histologie und Histopathologie des Nervensystems. Von Paul Schröder. S. 101. Jena: Gustav Fischer, 1908.

An excellent introduction to the study of the structure and pathology of the nervous system. The first four chapters, forming a half of the whole book, are devoted entirely to its normal histology, the rest to the principles of neuropathology. The manner in which most of the subjects are treated is admirable; the descriptive reviews, for instance, of the structure of the neuroglia and of the lymph supply of the central nervous system are remarkably clear and concise. As the author admits in his preface, his views have been largely determined by Nissl's teaching, a fact that should make this small book very valuable to English readers, from whom, on the whole, Nissl's work has scarcely received the attention it deserves.

Beiträge zur Pathologie des Stoffwechsels bei Psychosen (Erster Teil: "Die progressive Paralyse"). Von Dr. Max Kauffmann. Pp. 188. Jena: Gustav Fischer, 1908.

A careful investigation of the chemical changes in several cases of general paralysis of the insane under varying conditions. Patients were chosen in

various stages of the disease, and the weight, the nitrogen taken in and given out, and the water were determined. A case of general paralysis with aseptic fever, which the author believes to be caused by defective adaptation to sudden oxidation changes, and one where the patient was attacked with erysipelas were examined daily over considerable periods. A chapter is devoted to the condition of the blood and of the cerebro-spinal fluid obtained by lumbar puncture.

Beiträge zur Pathologie des Stoffwechsels bei Psychosen (Zweiter Teil: "Die Epilepsie"). Von Dr. MAX KAUFFMANN. Pp. 199. Jena: Gustav Fischer, 1908.

The same author investigated the nutrition in five cases of epilepsy by the same methods as he employed in cases of general paralysis of the insane. He also examined the blood and the cerebro-spinal fluid. A number of interesting observations are given, but he arrived at no definite conclusions with regard to the chemistry of this disease and its manifestations.

Reports from the Pathological Laboratory of the Lunacy Department of the New South Wales Government. Vol. I. Part III. With numerous figures. Pp. 167. Published by authority of the Government of the State of New South Wales. Sydney: W. A. Gullick, 1908.

This volume contains a study of the morphology of the brain of the Australian aboriginal by Dr. Flashman, and of the skull of the Australian aboriginal by Professor Hermann Klaatsch, of Breslau. Dr. Flashman's paper gives a naked-eye description of two brains, but the greater portion of the volume is taken up by the important monograph of Professor Klaatsch, illustrated with over a hundred photographs.

Mendel's Principles of Heredity. By WILLIAM BATESON, M.A., F.R.S. With 6 coloured plates and other illustrations. Pp. 396. Cambridge: University Press, 1909.

This book gives an account of discoveries in regard to heredity made by the application of Mendel's method of research. A translation of Mendel's two papers is appended, together with a biographical note. The case for Mendel's theory is stated with all Professor Bateson's well-known clearness of exposition, and its complexities are reduced to the simplest possible form. This book should be on the shelves of every medical man interested in the problems of heredity.

Einführung in die Lehre vom Bau und den Verrichtungen des Nervensystems. Von Prof. D. LUDWIG EDINGER. Mit 161 Abbildungen und 1 Tafel. S. 190. Leipzig: Vogel, 1909.

This is an admirable summary of our certain knowledge of the structure of the central nervous system set out clearly for students. The descriptions are clear and simple and the figures excellent. Any physician interested in neurology would find this little book an excellent means of refreshing his knowledge of the nervous system.

Diseases of the Nervous System for the General Practitioner and Student. By ALFRED GORDON, M.D. (Paris), A.M. With 136 illustrations. Pp. 487. London: H. K. Lewis, 1908.

An elementary text-book in which diseases of the nervous system are treated in the conventional manner. Most of the figures are taken from other books.

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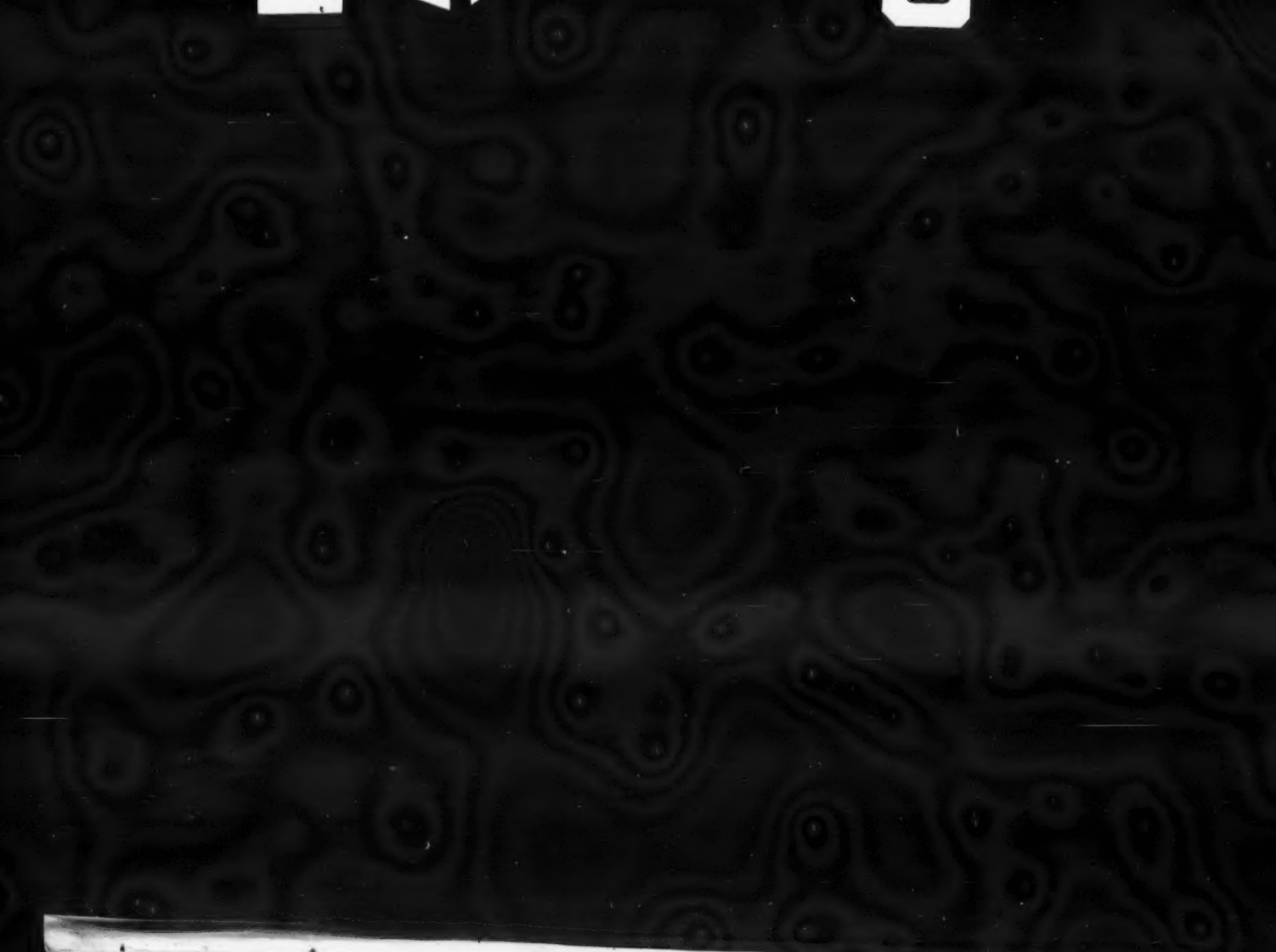
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